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DISEASES

of the

CHEST

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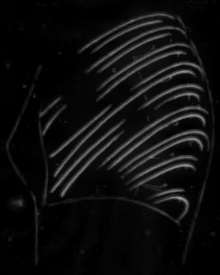

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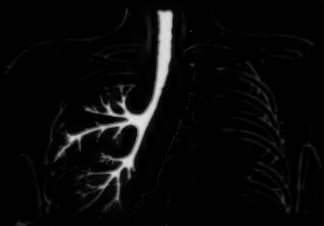

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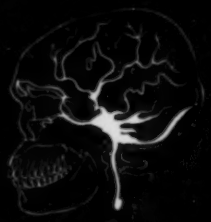

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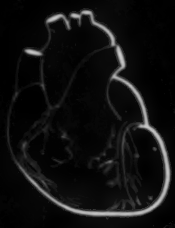

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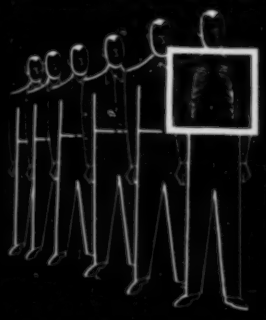

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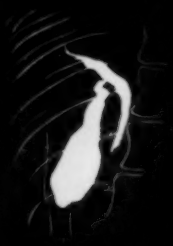

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Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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Peck, W. M.: Pub. Health Rep. 71:1159 (Dec.) 1956.

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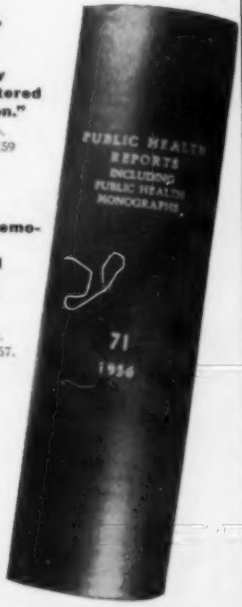
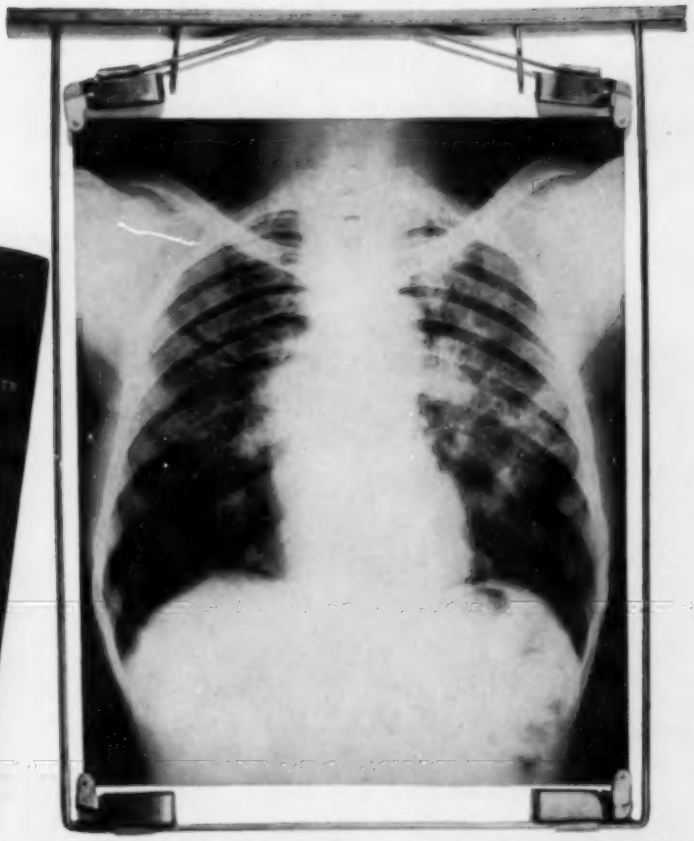
Chapman, P. T.: J. Kentucky M. A. 55:235 (March) 1957.





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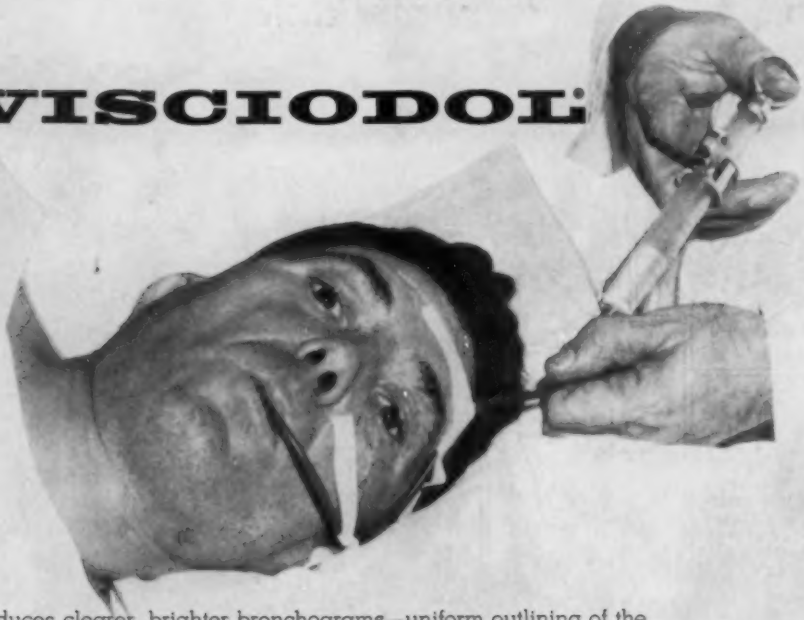

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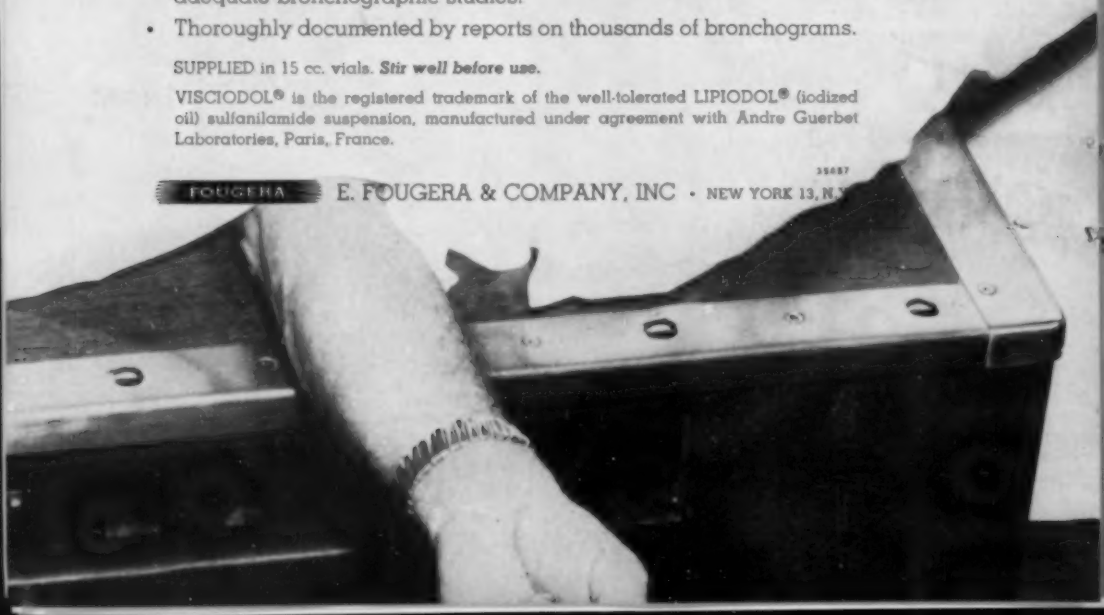

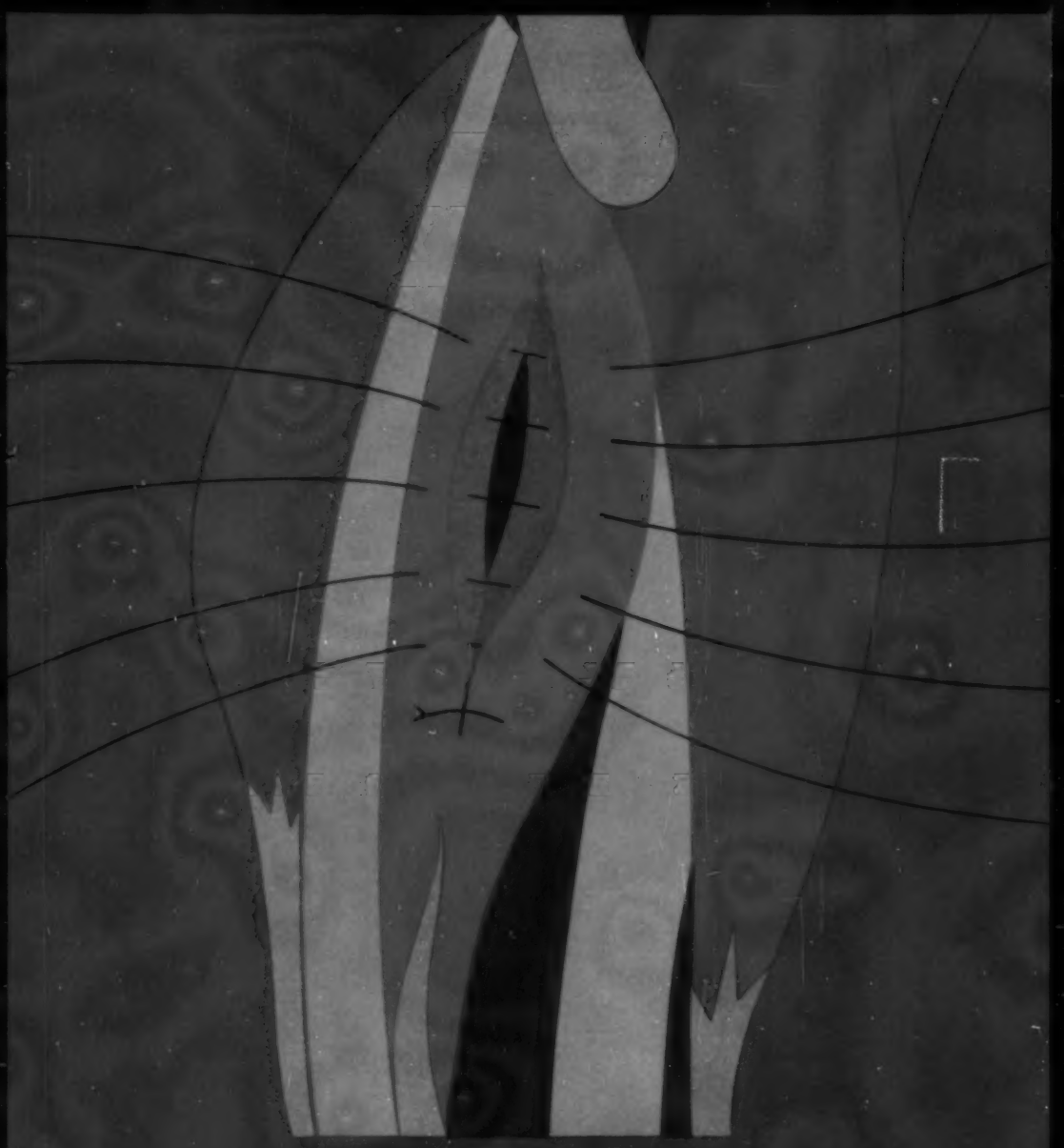

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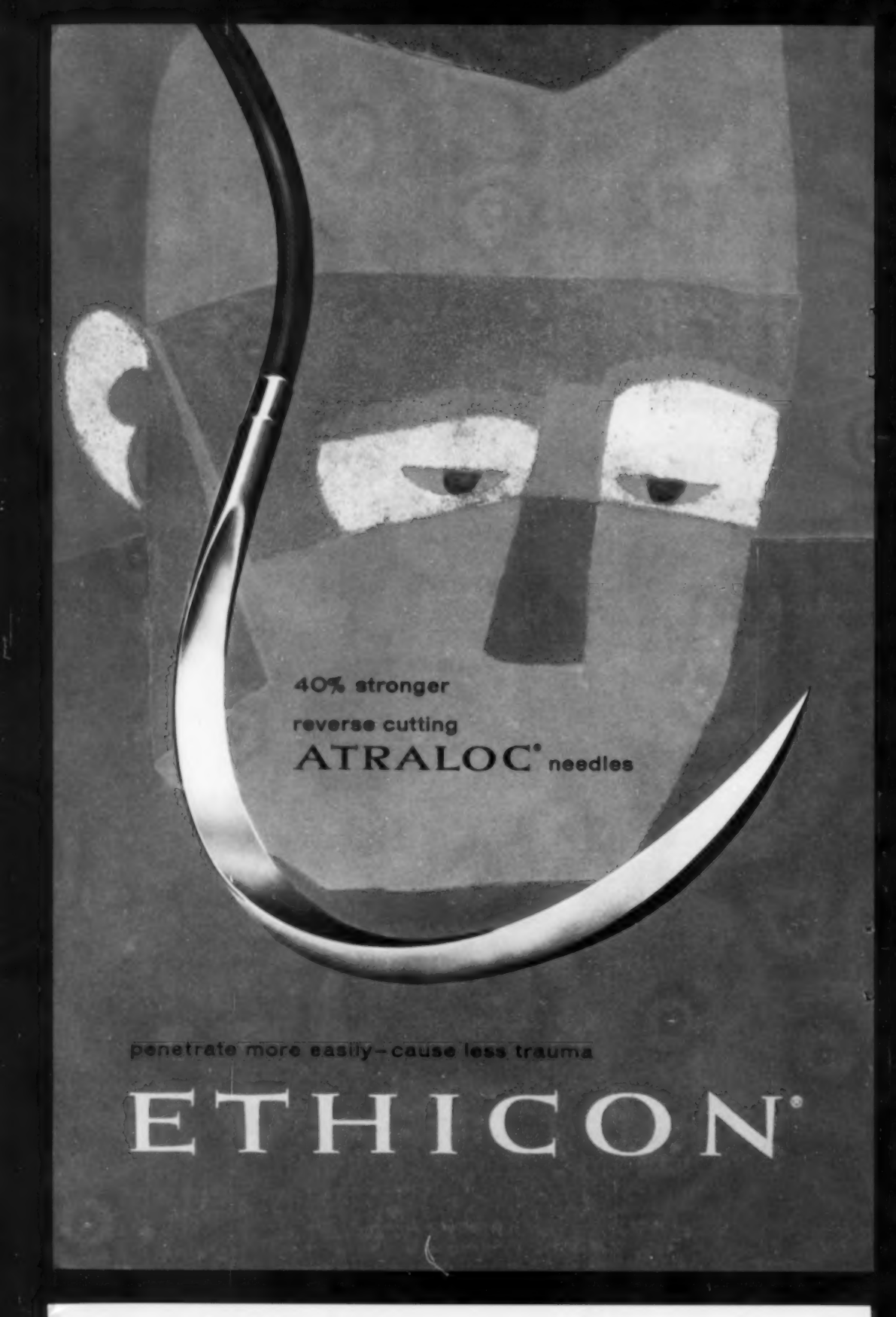
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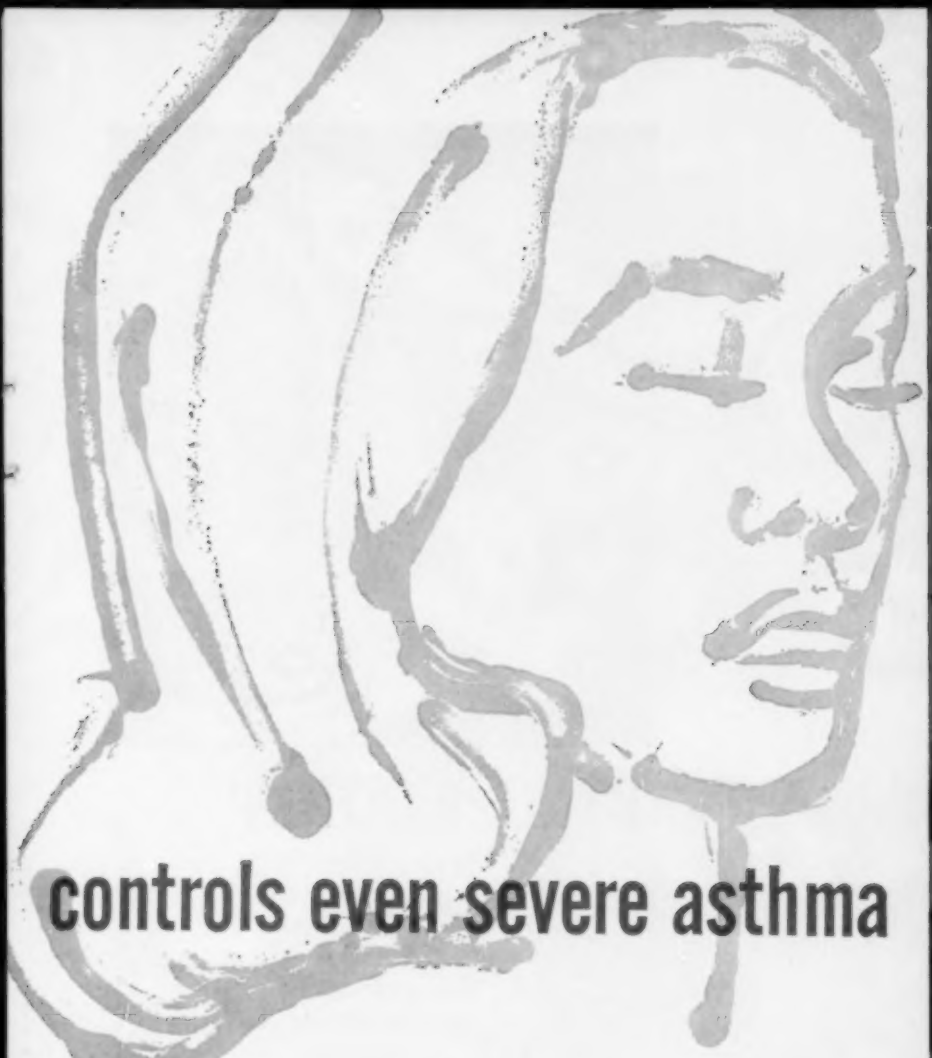

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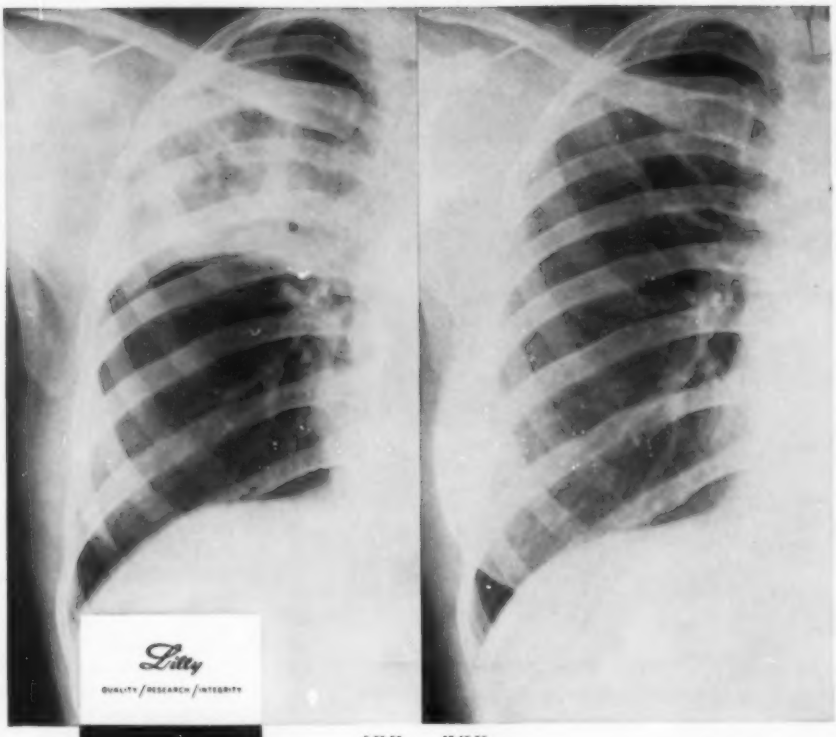

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DISEASES of the CHEST

VOLUME XXXII NOVEMBER, 1957 NUMBER 5

Histopathology of the Effect of Cortisone on the Irradiated Rat Lung*

CHARLES C. BERDJIS, M.D.** and REYNOLD F. BROWN, M.D.

San Francisco, California

Introduction

The histopathologic changes in the irradiated lung have been described previously.[1-3] However, since the pathogenesis is a continuous process, Brown[4] emphasized the need for experimental conditions to gain uniformity of dose and elapsed time after irradiation. He described the effects of irradiation on the rat lung and postulated the early pathogenesis as being one of bronchial obstruction followed by atelectasis. Cottier[5, 6] also came to the same conclusion in independent studies. Both authors studied the effects of various therapeutic agents on the reaction and cortisone was used in both experiments. Brown concluded that cortisone may have prevented atelectasis in some animals by inhibiting the general inflammatory reaction after irradiation, and by so doing, aeration of the lung was maintained. Cottier[6] stated that cortisone treatment diminished the tendency to fibrosis but led in some cases to lobular pneumonia and necrosis.

In the present studies with the rats of the earlier experiments,[4] our purpose is to describe in greater detail the histopathologic changes in the lung and to investigate as far as possible the effect of cortisone on the pathogenesis when given before and after irradiation.

Materials and Methods

Male and female FAC-F_1 rats were irradiated with 250-kv constant potential x-rays (HVL, 0.47 mm. Cu; tissue-dose rate, about 125 r/min.; target-animal distance, 70 cm.). A dose of 3000 r was administered to the right hemithorax in a single exposure. In order to evaluate the effects of cortisone, groups of animals were given cortisone three days before, 14 days after, and 28 days after irradiation. In repeated experiments the reactions of the animals were studied with a series of observations which included mortality, weight changes, serial roentgenograms of the thorax, bronchograms, arteriograms, venograms, and macroscopic and microscopic

*From the Radiological Laboratory, Department of Radiology, University of California School of Medicine, San Francisco. The Radiological Laboratory is one of the research and development installations of the United States Atomic Energy Commission.

**Presently Major, MC, USA, at Fourth U. S. Army Medical Laboratory, Fort Sam Houston, Texas.

FIG. 1

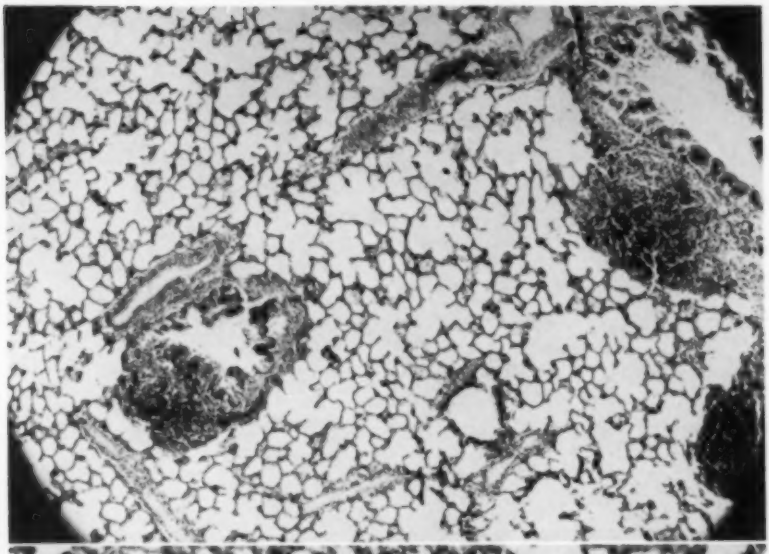

FIG. 2

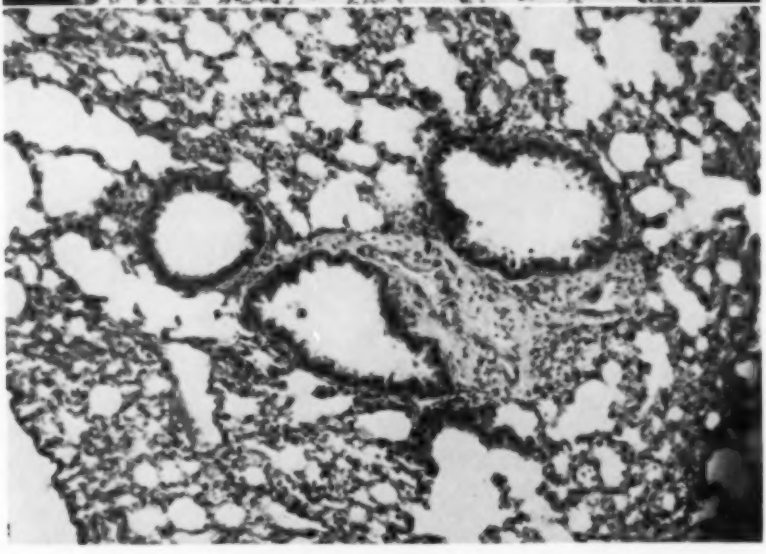

Figure 1: Section of a normal lung in an unirradiated, non-cortisone-treated rat showing the usual folding epithelium. A slight amount of fibrosis and peribronchial lymphoid infiltration are present. Hematoxylin and eosin stain. X 70.—*Figure 2:* Section of a normal lung in an unirradiated, cortisone-treated rat. The amount of peribronchial lymphoid tissue is considerably reduced compared with a normal, non-cortisone-treated rat (Fig. 1). The unexpected presence of the peribronchial fibrous tissue is due to the healing of pneumonitis which occurred during the experiment. Hematoxylin and eosin stain. X 100.

examination of the lungs. Further details have been given in a previous paper.[4]

The surviving animals were sacrificed and autopsied 90 days after irradiation; a few non-survivors were also autopsied at the time of death. The tissues were fixed in Bouin's fluid and were imbedded in paraffin. Sections were stained with hematoxylin and eosin, and also with other stains such as Masson, Van Gieson, Mallory, and/or Weigert elastin stain.

For purposes of microscopic examination, sections from the lungs of the following groups of animals were selected; the number of animals examined in each group is given in parentheses.*

1. Irradiated, no cortisone treatment (18)
2. Irradiated, cortisone treatment (31):
   Subgroups: Cortisone administered before irradiation (20)
   Cortisone administered after irradiation (11)
3. Controls (10):
   Subgroups: Non-irradiated, no cortisone treatment (6)
   Non-irradiated, cortisone treatment (4)

Results

Microscopic Examination: The microscopic studies** concern (1) the irradiated lung of the non-cortisone-treated rat, including the relationship between bronchial obstruction and degree of atelectasis, and (2) the irradiated lung of the cortisone-treated rat.

Irradiated Lung of Non-Cortisone-Treated Rat: Sections from the irradiated right lung of animals not treated with cortisone showed uniformly the same histopathologic change, namely atelectasis (Figs. 3 and 4). In a majority of cases, the bronchial epithelium was not folded as in the normal rat, and had lost its villi. Atrophy, with a non-ciliated, flattened epithelium was the rule. Some bronchi were collapsed, with more or less obliteration, and a partial resorption of the bronchial wall. The latter, containing degenerative epithelium, was generally melted into an extensive peribronchial fibrosis (Fig. 3).

Occasionally the bronchial epithelium showed a more or less marked proliferation with metaplasia (Fig. 4). In these instances, in contrast to those mentioned above, the proliferated and squamous bronchial epithelium appeared to be somewhat papilliferous.

*Some of these animals had also been given Terramycin, but histologically it had no effect on the lung.

**The structure of the normal rat lung differs from that of man in the following respects: (1) There are five pulmonary lobes, one in the left and four in the right lung (apical, cardiac, azygotic, and one small intermediate caudal). (2) The right main bronchus is short, and with the trachea forms a right angle, while the left main bronchus descends obliquely into the hilus of the left lung. The right main bronchus near its origin divides into a shorter main bronchus (epi-arterial) for the apical lobe. (3) The pseudostratified bronchial epithelium is frequently folded, with a cryptic arrangement. (4) The C-shaped cartilage of the trachea and the fragmented cartilage of the main bronchi disappear when the bronchi enter the lung. (5) The alveolar walls contain a varying number of lymphocytes and, occasionally, granular leukocytes. (6) The adventitia of the large pulmonary vessels (particularly the veins and occasionally the venules) are reinforced by a normal more or less thick layer of striated muscle connected with cardiac-type muscle fibers.

FIG. 3

FIG. 4

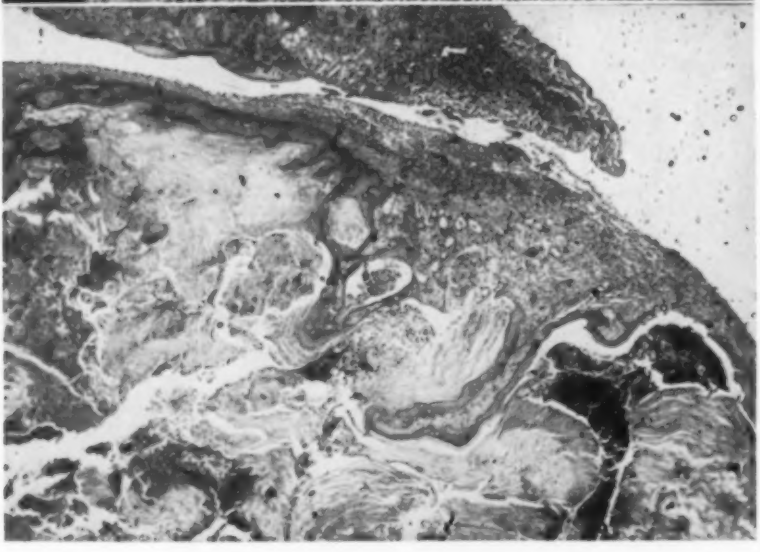

Figure 3: Section of the irradiated lung in a non-cortisone-treated rat showing complete atelectasis. Note the extensive perivascular, peribronchial, and alveolar fibrosis. Purulent bronchitis and diffuse inflammatory reaction may be observed. The amount of perivascular and peribronchial lymphoid tissue is unchanged. Hematoxylin and eosin stain. X 80.—*Figure 4:* Section of the irradiated lung in a non-cortisone-treated rat showing proliferative stratified epithelium (squamous metaplasia) with cornified lamella and pearls which, together with the inflammatory cells, contributed to the occlusion of the main bronchus. The lobule (at top of picture) is entirely atelectatic. Hematoxylin and eosin stain. X 35.

Fibrosis was directly related to atelectasis and appeared to be of two types (Fig. 3) : (1) fibrous tissue with diffuse round-cell infiltration resembling scar tissue, interpreted as a vestige of chronic pulmonary infection (Fig. 2), and (2) fibrous tissue with some collagen and scattered elastin fibers (Fig. 3). This was sometimes intermingled with inflammatory cells generally containing fragmented debris of bronchial walls, and occasionally foreign body giant cells. Whereas the first type of fibrosis is commonly present in non-irradiated rats suffering from pulmonary infection* (compare Fig. 2 with Fig. 3), the second type is attributed only to the radiation syndrome. The fibrosis usually extended to the wall of the alveoli, particularly in the areas of reduced aeration (Fig. 3).

The lumens of some bronchi contained debris or degenerative cells, rare blood cells, and occasionally a few macrophages and/or leukocytes. Blood pigments were not infrequent (Fig. 3).

The trachea was involved in the bronchoalveolar changes, but it was never obliterated. Narrowing of the trachea was found in some animals.

Acute, subacute, or chronic inflammatory reaction was frequent, producing either pneumonitis, bronchopneumonia, bronchitis, or bronchitis with abscess. In the abscessed areas, degenerative epithelial cells and dilation of the bronchi were frequently observed.

The alveoli were extensively involved in the inflammatory reaction, forming both red and gray hepatization, partly organized. The alveolar wall was thickened by fibrous tissue in which some obliterated capillaries were visible. The responsible bronchi were partly or entirely collapsed or obliterated, and a peribronchial cuff or ring of extensive fibrous tissue was apparent (Fig. 4). The alveolar wall failed to show the hyalinization considered to be pathognomic by certain authors.[3] However, in two or three instances, fragmentary hyalinized particles were observed intermingled with fibrous tissue.

Relationship Between Bronchial Obstruction and Degree of Atelectasis: Bronchial obstruction of all degrees was found in the irradiated, atelectatic lung, associated with fibrosis, degenerative and inflammatory changes, abnormal metaplasia, and epithelial proliferation (Fig. 4). Atelectasis, partial or total, depended on the site of the obstruction.

The *main bronchus* was particularly obstructed when there was an abnormal papillary or squamous metaplasia with superposed parakeratosis or cornoid lamella (Fig. 4). The latter, composed of extensive concentric layers forming the large pearls or diffuse cornified zones, occluded not only the main bronchus but involved the adjacent part of the trachea. Usually this kind of bronchial obstruction was accompanied by an extensive, acute inflammation.

*One frequently finds in the so-called normal rat epizoötic infections such as pneumonia, bronchopneumonia, bronchitis with abscess, and eventual interstitial chronic pneumonitis. These conditions occasionally occurred in our animals; in some of the lungs examined a status of morbidity posed a thorny problem in the interpretation of some post-irradiation changes such as fibrosis—particularly in the irradiated, non-atelectatic lung of a cortisone-treated rat. However, the acute pulmonary infections with high mortality described by Nelson[7] and by Innes et al.[8] were rare or non-existent in our animals.

FIG. 5

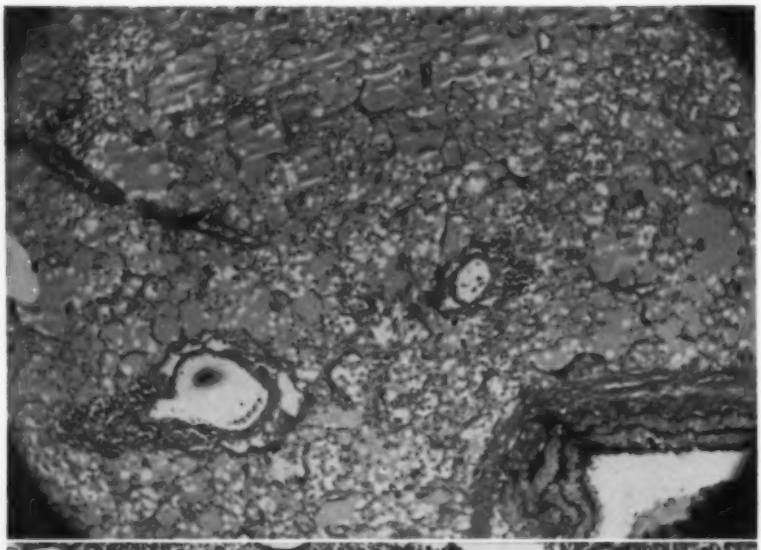

FIG. 6

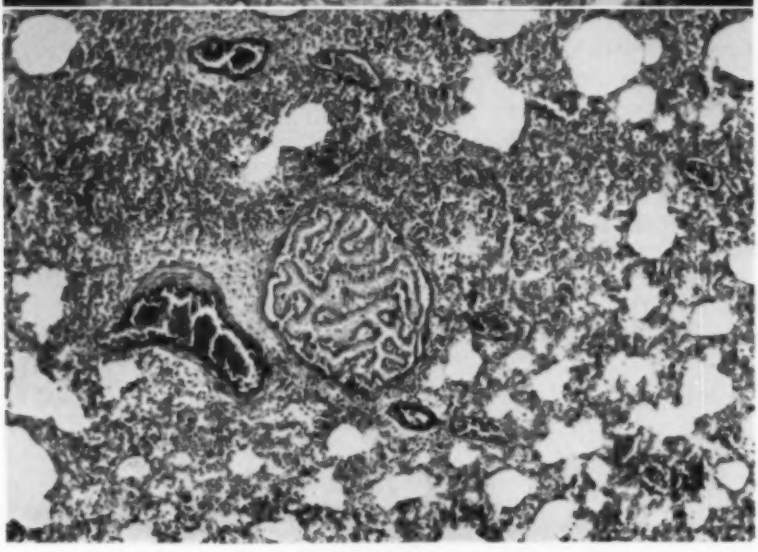

Figure 5: An example of atelectasis in the irradiated lung of a cortisone-treated rat, showing the dilated alveoli filled with a large amount of sero-fibrino exudate (liquefaction). A small amount of fibrous tissue may be seen around the blood vessels and the bronchi. No inflammatory reaction is present. There is much less lymphoid tissue than in the normal lung (Fig. 1). Van Gieson and Weigert elastin stain. X 100.—*Figure 6:* Section of the irradiated lung in a cortisone-treated rat. This lung was partly atelectatic (upper portion) and partly aerated (lower portion). Adenomatous proliferation of the bronchial epithelium has obliterated a relatively small bronchus. Only a few lymphoid cells and slight fibrosis are present around the bronchovascular tree. Hematoxylin and eosin stain. X 100.

The *medium-sized bronchi* were occluded chiefly by inflammatory reaction and/or degenerative changes of the epithelium, and occasionally by bronchogenic papillary adenomatous formations (Fig. 5).

The *small bronchi* and the bronchioles might be occluded by any abnormal changes, including inflammation, metaplasia, or proliferative papilliferous formation. In general, fibrosis played an important role in occluding the small and medium-sized bronchi. If the main or medium-sized bronchi were not obliterated but the small bronchi were, there was formed the patchy atelectasis described by some investigators. This patchy atelectasis is not necessarily due to irradiation; it was also found in the non-irradiated controls who suffered some inflammatory pulmonary condition.

Irradiated Lung of Cortisone-Treated Rat: The study of the irradiated lungs of cortisone-treated rats indicated that time of treatment affected the histopathologic changes in the lungs observed 90 days after irradiation. In the three cortisone treatment groups (three days prior to, two weeks after, and four weeks after irradiation) there was a variability of histopathologic effect, and the characteristic conditions for each treatment group are described. However, two extreme conditions were found in all three groups, (1) the well aerated lung and (2) the completely atelectatic lung.

(1) The well-aerated lung in the cortisone-treated rat differed in some respects from the well-aerated lung in the non-cortisone treated. The parenchyma had well-defined alveolar sacs and bronchi with normal epithelium. The alveolar walls were thin and devoid of fibrosis. Fibrosis was confined in small amounts about the bronchovascular trees. (However, our control animals, because of pneumonitis, had a greater amount of fibrosis than found in the normal animal.) Some portions of the pleura and septa were slightly thickened by fibrous tissue, with a few scattered elastic tissue fragments, interpreted as vestiges of the effect of irradiation. The peribronchial and perivascular lymphoid tissue was considerably reduced, and the wandering round cells of the alveolar walls were usually absent. In such lungs no inflammatory reaction was observed.

(2) The atelectatic lung in the cortisone-treated rat differed from the atelectatic lung in the non-cortisone-treated by a characteristic change in the histologic appearance of the atelectasis. Most of the alveolar cavities were dilated and filled with transudates or sero-exudate fluid (Fig. 5). This diffuse and extensive edema-like liquid or "liquefaction,"* homogeneously stained with the usual stains, contained nothing or occasionally a few red blood cells, rare macrophages, and/or rare inflammatory cells. No fibrin was noted in this fluid material. Hyperemia, stasis, intense congestion, or hemorrhage, present in most cases, seemed to increase considerably the degree of atelectasis. However, with an occasional exception, inflammatory reaction was not marked. Abscesses, bronchopneumonia, and/or bronchitis, usual in the irradiated lung, were infrequent or absent. Degenerative bronchial epithelial cells and desquamation were present in

*"Liquefaction" is used in this paper to designate a condition resembling acute edema of the lung, with diffuse serous exudate and/or transudates.

all cases (Fig. 5). Fibrosis was moderate and limited about the bronchi and the vessels. Peribronchial and perivascular lymphoid tissue was highly reduced. In some places the pleura appeared to be more or less thickened by scattered fibrous tissue. The cells of the alveolar wall had undergone hydropic degeneration and were partly destroyed.

In addition to the two general effects described above, there were lungs showing variations according to the time of cortisone administration.

Cortisone Treatment Three Days Prior to Irradiation: The greatest number of the well-aerated lungs described above were found in this treatment group. The remaining lungs in this group showed partial or patchy atelectasis which extended over several lobules. If partial aeration remained at the edges of some lobules, there was generally compensatory emphysema. Diffuse or focal liquefaction, together with hyperemia, stases, and/or hemorrhage, were present in the atelectatic parenchyma. Inflammatory reaction, however, was not marked. Abscesses, extensive bronchopneumonia, and/or bronchitis, usual in the irradiated lungs, were absent. Degenerative epithelial cells of the bronchi and desquamation were usually present. Fibrosis was moderate and limited about the bronchi and vessels, and occasionally the pleura or septa. Peribronchial and perivascular lymphoid tissue was much reduced.

Cortisone Treatment Two Weeks After Irradiation: In this group, the lung parenchyma had diffuse zones of atelectasis intermingled with well-aerated alveoli (Fig. 6). Again, liquefaction was diffuse or focal and generally marked in the atelectatic areas. In contrast with non-cortisone treated animals, the alveolar walls were mostly devoid of fibrosis. There was moderate, fragmented fibrosis in only a small group of alveoli, in which no liquefaction was apparent. The folding epithelium in the bronchi was mostly proliferated, with some areas of papillary formation (Fig. 6). Peribronchial lymphoid tissue was reduced in the very small foci. Fibrosis was less marked than in the atelectatic lungs of non-cortisone-treated animals. A generalized hyperemia was contrasted with relatively well-marked, striated, cardiac-like muscle fibers around the vessels. The total process appeared more diffuse than in the cortisone group treated three days before irradiation.

Cortisone Treatment Four Weeks After Irradiation: Atelectasis was the predominant picture in this group, with a few small zones showing aeration. Apart from total or partial liquefaction, the parenchyma showed rather marked infection resulting in red or gray hepatization, with some degree of necrosis and occasional abscess formation. In some preparations pleura and/or septa were thickened by fibrosis, and in others the alveolar wall showed fragmented fibrosis. The bronchial walls showed resorption and desquamation, and there was an accumulation of fluid containing many inflammatory cells in the lumens. The above findings are summarized in Table I.

Discussion

Studies of mortality, body-weight changes, serial thoracic roentgenograms, and macroscopic observations 90 days after irradiation showed

that cortisone administration may change the effects of irradiation in the rat lung. Histologically, the changes were even more striking.

In animals that were irradiated and given cortisone, the change in the irradiated lung parenchyma evolved in a distinctive manner: the total atelectasis was replaced by (1) total or partial aeration and (2) total or partial liquefaction. Liquefaction, inhibition of inflammatory reaction and lymphoid tissue, and reduction of fibrosis were sufficient to allow identification of these sections when they were treated as unknowns. No other treatment procedures (irradiation alone, cortisone alone, Terramycin alone, or a combination of these drugs) or spontaneously occurring infection reproduced this characteristic picture.

From the analysis of the histopathologic observations, it appears that cortisone is not curative, but in some cases it prevents the occurrence of atelectasis.

The difficulty in assessing the pharmaceutic and physiologic activity is the variability in the response of the lung parenchyma. Cortisone probably acts as a therapeutic agent by inhibiting the inflammatory reaction at the cellular level. It also inhibits the reaction to secondary infection, thus decreasing the production of fibrosis. However, although cortisone inhibits the inflammatory reaction and reduces the amount of lymphoid tissue and the production of fibrosis, it may be responsible for the liquefaction.

Liquefaction is not observed as an effect of cortisone treatment alone, but of irradiation plus cortisone treatment. It is possible that cortisone acts against the effects of irradiation in producing liquefaction. The nature and the mechanism of the production of liquefaction, however, could not be determined. Microscopically it resembles acute pulmonary edema or transudates, but it is not an inflammatory edema because it does not

TABLE I
CHANGES IN IRRADIATED LUNG OF ANIMALS TREATED WITH CORTISONE

Observation	No Cortisone (Irradiated Controls)	Cortisone Administration		
		Day 3 before irradiation	Day 14 after irradiation	Day 28 after irradiation
Atelectasis	Subtotal or total	Partial or none	Usually more marked than on day 3; occasionally none	Subtotal or total
Inflammatory reaction	Frequent	None or occasional	None or occasional	Less frequent than in irrad. controls; more frequent than in other cortisone groups
Abscess	Extensive	None	Occasional	Infrequent
Lymphoid tissue	Unchanged (same as normal)	Less than irrad. controls	Less than irrad. controls	Unchanged, or less than irrad. controls
Liquefaction	None	Always present in atelectatic lung	Diffuse. Always present in atelectatic lung	Partial or total

contain fibrin and inflammatory cells. It could not be determined either if this process played a role in maintaining aeration.

Cortisone may also act by increasing the capillary pressure or its permeability, leading to a passive hyperemia found frequently. It is suggested that liquefaction could be a result of this increased permeability. The question arises as to whether liquefaction is to be considered as a late necrosis destroying the lung parenchyma and replacing the true atelectasis, or as an intermediate stage leading to aeration and thus a beneficial reaction. More investigation is required to answer this question.

The time of cortisone administration also seemed to play an important role. The preventive action of cortisone was more efficient when it was given three days before irradiation rather than later (Table I).

SUMMARY

The radiation reaction in the rat lung produced by a single exposure (3000 r) to the right hemithorax was characterized 90 days after irradiation by atelectasis, extensive or diffuse fibrosis, frequent infection, metaplasia, and occluded bronchi.

The irradiated lung responded to cortisone treatment in two ways: there were degrees of reaction varying from well-aerated to completely atelectatic lungs.

The most interesting finding was that the atelectasis in irradiated, non-cortisone-treated rats was different from that in irradiated, cortisone-treated rats. In the latter, cortisone treatment led to the production of liquefaction in the atelectatic lung parenchyma. The nature of the liquefaction could not be determined.

Histopathologic studies confirmed the earlier conclusion that when cortisone treatment had a beneficial effect it was more apparent if cortisone was given three days before irradiation and possibly during the first two weeks after irradiation rather than later.

Cortisone reduced the amount of fibrous and lymphoid tissue in the irradiated lung and inhibited inflammatory reaction, regardless of the time of its administration.

RESUMEN

La reacción a la radiación en el pulmón de la rata, producida por una sola exposicion (3000 r) en el hemitórax derecho, se caracterizó por la aparición 90 días después de atelectasia, fibrosis extensa o difusa, infección frecuente, metaplasia y oclusión bronquial.

El pulmón irradiado respondía al tratamiento con cortisona de dos maneras: hubo grados variables de reacción desde bien creados hasta pulmones completamente atelectásicos.

El hallazgo más interesante fué que la atelectasia en las ratas no tratadas con cortisona fué diferente de la que se observó en las tratadas con cortisona.

En estas últimas el tratamiento con cortisona condujo a la liquefacción

del parénquima pulmonar atelectásico. La naturaleza de la liquefacción no se pudo determinar.

Los estudios histopatológicos confirmaron la anterior conclusión de que cuando el tratamiento con cortisona ha tenido efecto benéfico, éste es aparente si la cortisona es dada tres días antes de la irradiación y posiblemente durante las primeras dos semanas después de la irradiación mejor que más tarde.

La cortisona redujo la cantidad de tejido fibroso y linfoide en el pulmón irradiado e inhibió la reacción inflamatoria sin tener en cuenta el tiempo de su administración.

RESUME

Une seule exposition à une irradiation par les rayons X de 3000 R sur l'hémithorax droit du rat produisit 90 jours après une série d'altérations. Celles-ci comportaient de l'atélectasie, une fibrose extensive ou diffuse, de l'infection fréquente, une métaplasie et une obstruction des bronches.

Le poumon irradié répondit au traitement cortisonique de deux façons avec des degrés variant depuis les poumons bien áerés jusqu'aux poumons complètement atélectasiés.

La constatation la plus intéressante fut que l'atélectasie chez les rats irradiés, non traités par la cortisone, se comporta de façon différente de celle des rats irradiés et traités par la cortisone. Chez ces derniers, le traitement par la cortisone amena une liquéfaction dans le parenchyme pulmonaire atélectasié. La nature ne put en être déterminée.

Des études histoplathologiques confirmèrent les conclusions antérieures: l'effet favorable du traitement par la cortisone fut plus marqué quand la cortisone avait été utilisée trois jours avant l'irradiation, et si possible les deux premières semaines qui suivirent cette irradiation plutôt que dans les cas où le traitement fut plus tardif.

Sans tenir compte du moment où elle fut administrée dans l'ensemble la cortisone réduisit la quantité de tissu fibreux et lymphoïde dans le poumon irradié, et inhiba la réaction inflammatoire.

ZUSAMMENFASSUNG

Die Strahlen-Reaktion der Rattenlunge aufgrund einer einzigen Exposition (3000 r) des rechten Halbthorax war gekennzeichnet neunzig Tage nach der Bestrahleung durch Atelektase, ausgedehnte oder diffuse Fibrose, häufige Infektion, Metaplasie und Bronchialverschluss.

Die bestrahlte Lunge beantwortete die Cortison-Behandlung auf doppelte Weise: Es bestanden Reaktionsgrade variierend von gut durchlüfteten bis zu komplett atelektatischen Lungen. Der am meisten interessante Befund bestand darin, dass die Atelektase bei bestrahlten, nicht mit Cortison behandelten Ratten abwich von derjenigen bei bestrahlten, aber mit Cortison behandelten Ratten. Bei letzteren führte die Cortison-Behandlung zum Auftreten einer Einschmelzung in dem atektatischen Lungenparenchym. Die Natur der Einschmelzung konnte nicht bestimmt werden.

Histopathologische Untersuchungen bestätigten den früheren Schluss, wonach—sofern die Cortison—Behandlung einen nützlichen Effekt hatte dieser stärker in Erscheinung trat, wenn Cortison 3 Tage vor der Bestrahlung gegeben wurde und vielleicht eher während der ersten beiden Wochen nach der Betrahlung als später.

Cortison verringerte das Mass von Bindegewebe und Lymphgewebe in der bestrahlten Lunge und hemmt die entzündliche Reaktion unbeschadet des Zeitpunktes seiner Anwendung.

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The Electrocardiogram and Vectorcardiogram of the Normal Infant

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During the past two and one half years we have been making serial studies of infants' electrocardiograms and vectorcardiograms. The subjects were obtained from the Well Baby Clinic of Touro Infirmary at the ages from one day to one month and are being restudied at intervals of from one to three months during the first year of life and every six months thereafter. It is hoped that in this way data might be obtained that is free of some of the difficulties involved in parallel studies.

Obviously, the most important application of these studies relates to the diagnosis of congenital heart disease. Since some congenital lesions are not evident until the child is older final evaluation of the data of this kind of study must await the passage of time. However, a large number of such observations made on infants who have attained the age of two and one-half years without showing evidence of abnormality deserves some attention.

The present paper, based upon serial observation of 300 infants, reports only those findings of general clinical interest from the standpoint mentioned above. Studies of the ventricular gradient as an expression of the QRS-T relationship will be reported later.

Method

Electrocardiograms (Leads I, II, III, aVr, aVl, aVf, V4r, V1, V2, V4, V6) were recorded with a four channel direct writing apparatus. Vectorcardiograms were recorded first with a dual beam oscilloscope equipped with proper preamplifiers and more lately with the Sanborn vectorcardiograph. The cube (Grishman) and tetrahedron (Wilson) frames of reference were both employed.

Results

QRS Complexes of the Limb Leads and the Frontal Plane QRS Loop

The limb potentials may be recorded either as the standard and unipolar limb leads or as a frontal plane vector loop. This loop, recorded by applying the potentials of lead I to the X axis and the potentials of lead Vf (multiplied by V3) to the Y axis of the oscilloscope, is the frontal plane loop of the tetrahedron frame of reference. The leads can be constructed from the loop and the loop can be constructed from the leads in a simple

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manner (Fig. 15). Consequently the limb leads and the frontal plane loop described above will be discussed together.

The frontal plane loops of infants in the first few days of life are usually inscribed clockwise and are directed downward and to the right with the terminal portion of the loop coursing upward and to the right. Lead I, therefore, consists of a small R wave followed by a relatively deep and wide S wave, while Leads II and III usually consist of large R waves followed by S waves (Figs. 1 and 2). Small Q waves frequently occur in Leads II and III but may also be seen in Lead I. Individual variations are common. For example Figure 3A shows the frontal plane QRS loop beginning counterclockwise and lying approximately on the 90 degree axis so that there is almost no QRS deflection in Lead I. In most individ-

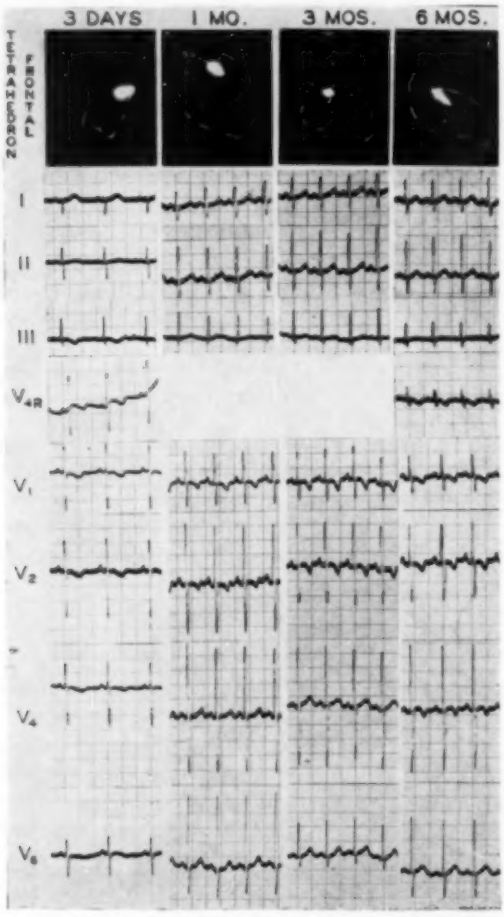

FIGURE 1: Typical serial electrocardiograms and corresponding frontal plane vectorcardiograms of a normal infant. A gradual swing of the QRS loop to the left with an increase in the R wave and diminution of the S wave is seen in Lead I.

uals the QRS loop and complexes of the extremity leads are of smaller magnitude and duration than they are a few months later. Shortly after birth the QRS duration is about 0.04 seconds and increases to about 0.065 seconds by the end of the first year.

Shortly after birth the electrocardiogram and the frontal plane loop begin a progression of changes which eventually culminates in the normal adult pattern. Considerable individual variation is encountered in the rate of change, but usually the degree of right axis deviation diminishes progressively during the first few months of life. Figure 1 illustrates the change most commonly seen. At the age of one month the frontal plane loop still lies largely to the right, but less so than in the newborn. Correspondingly we see larger R waves and relatively smaller S waves in Leads I and II. If a pronounced S wave had been present in Lead II at birth it usually also diminishes.

After the age of one month even greater individual variation is seen. Although some infants at three months still show the pattern commonly

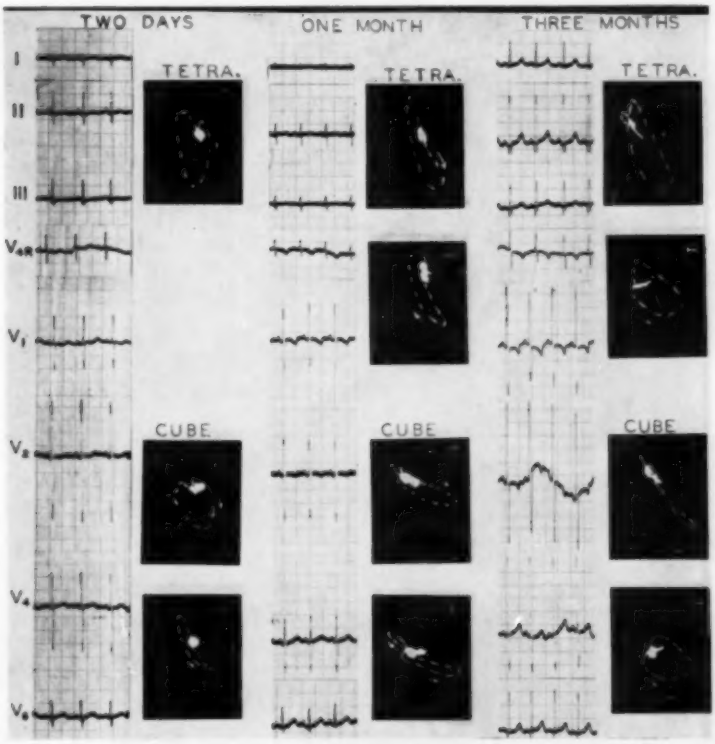

FIGURE 2: Serial electrocardiograms and vectorcardiograms illustrating the changes seen during the first three months of life. The frontal plane QRS loop is inscribed more to the left and the horizontal QRS loops recorded with the cube system changes from clockwise inscription at two days, to a figure-of-eight loop at one month, and to a counterclockwise loop at three months of age.

seen at one month the entire frontal plane QRS loop usually lies further to the left than at one month (Figs. 1 and 2) so that little or no S wave may remain in Lead I. This finding is in disagreement with Ziegler[1] who states that "In Lead I, the amplitude of S remains large until at least three years of age and then decreases gradually, reaching adult proportions at the age of about twelve to sixteen years." Still other infants no longer have the clockwise vertical QRS loop but instead have counterclockwise loops directed much further to the left as reflected in the limb leads of Figure 4. Left axis deviation is not rare.

The number of infants with marked right axis deviation diminishes greatly after the age of three months although occasionally a mean QRS axis of 110 to 120 degrees persists throughout infancy.

After the age of three months there is generally less rapid change in the electrocardiogram and vectorcardiogram than that which characterized the first three months of life. Again much individual variation in the rate of change is evident. Figures 5 and 6 illustrate the changes that occurred in different individuals. Note that in Figure 5 there was a progressive change of the mean QRS axis to the left and a gradual decrease in the S

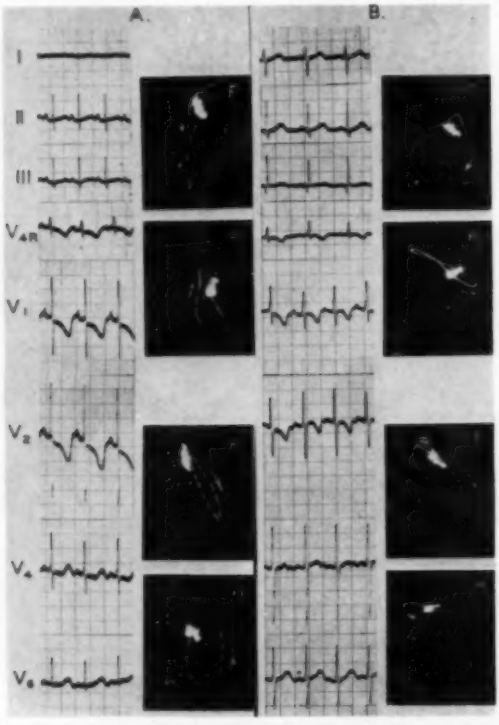

FIGURE 3: Electrocardiograms and vectorcardiograms of two normal infants illustrating the extremes of variation encountered. The horizontal plane QRS loop recorded with the cube system of the twenty-four hour old infants (A) is inscribed counterclockwise while that of the two year old infant (B) is inscribed clockwise.

wave in Lead I, while in Figure 6 there is essentially no change in the electrocardiogram from the age of one month to two years of age.

It might be well to add that an apparent slight increase in right axis deviation is occasionally observed in one record of a serial study which diminishes again in the succeeding observation. This is attributed to a slight change in rotation such as is commonly seen also in adults. With this apparent exception no regression toward more infantile forms is ever seen in normal subjects.

The QRS Complexes of the Precordial Leads

The evolution of change which occurs in the right precordial leads (V4r and V1), in the middle precordial leads (V2 and V4), and the left precordial leads (V6) will be described separately.

Shortly after birth V4r usually consists of a large R wave followed by a small S. Occasionally the R and S are of equal magnitude. In other in-

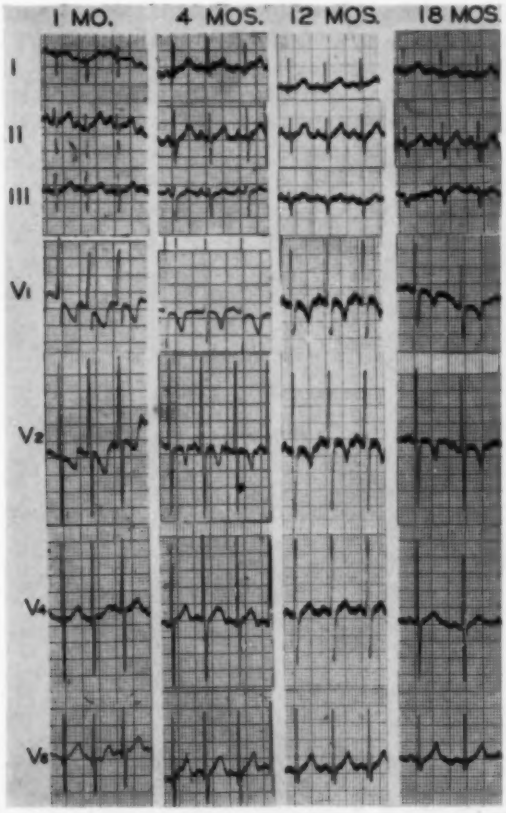

FIGURE 4: Serial electrocardiograms demonstrating a change from marked right axis deviation at one month to marked left axis deviation at four months of age. Such marked shifts in axis are not unusual when the heart is in an apex-back electrocardiographic heart position.

dividuals no S wave is present. Only exceptionally is a small Q seen in this lead. The deflections of V1 are usually similar to those of Lead V4r but the R and S waves are generally of greater magnitude. Most often the R in V1 is not as large in proportion to the S as it is in V4r. It is to be noted that the QRS complexes of these two leads at birth are almost always of smooth contour; notched complexes are unusual in these leads at this age.

At the age of one month V4r and V1 may have changed little, the R and S waves may both have increased proportionately in magnitude or the R wave may have become smaller and the S wave deeper. In some individuals a small Q wave may be seen and contrary to most previous reports, may persist throughout infancy (Fig. 7). A notch in the R wave or less frequently in the S wave, is not uncommon in these leads. Such notching is seen more frequently in V4r than in V1. It may be so marked that an RSR' complex results.

As infants become older several different types of changes occur in the precordial leads. Some subjects show little change throughout infancy (Fig. 6) and even at the age of two years still have the high R waves and small or no S waves in Leads V4r and V1 (Fig. 8A). Other infants who earlier had smooth unnotched RS complexes in the right precordial leads develop notched R waves even to the extent of the RSR' type of complex (Fig. 9). It is interesting that a similar series of events has been

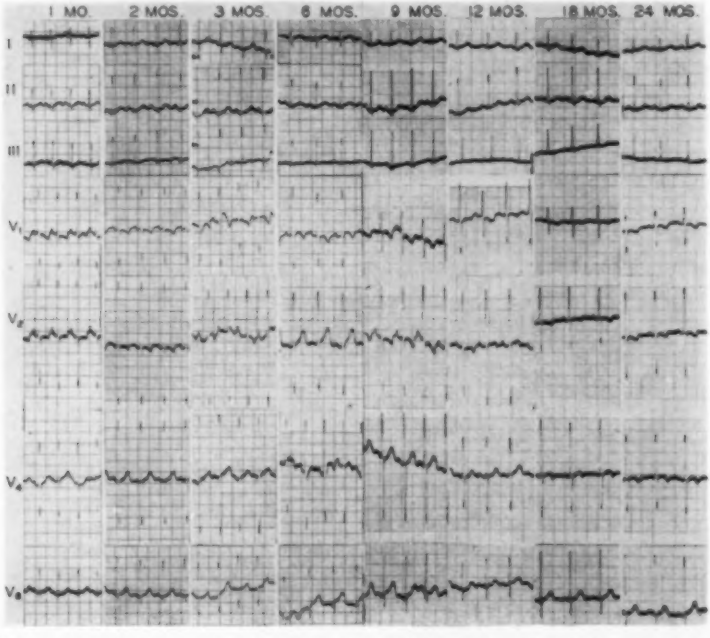

FIGURE 5: Typical electrocardiograms of an infant from one to twenty-four months of age. A gradual increase in R_1 and decrease in S_1 occurred during the first year of life with little change the second year of life.

described[2-4] following surgical correction of congenital heart disease in which right ventricular hypertrophy is present. The most frequent change that occurs in these leads through infancy involves a gradual decrease in the height and duration of the R wave and a gradual increase in the depth and duration of the S wave. Figure 8 demonstrates the marked difference that may be encountered in different individuals at the age of two years. Note that V4r and V1 of Figure 8A are similar to those of newborns while in Figure 8B the small R and larger S are similar to those of adult records.

At times an apparently regressive increase in the height and duration of the R in V4r and V1 is seen in one observation of a series which diminishes again at the next observation. Such apparently regressive changes are attributed to change in cardiac rotation or to difference in placement of the electrodes.

Leads V2 and V4 throughout infancy are characterized by large R and large S deflections. A small Q wave may be present in either or both leads. No remarkable serial change is seen in these leads. Occasionally the QRS complex in one or both of these leads attains large amplitude (Fig. 10). It is important to recognize that this may be a normal finding for some have attributed it to ventricular hypertrophy.

During the first few days of life Lead V6 usually consists of a small R wave and a relatively deep S wave. A small Q wave is frequently present. Occasionally no R wave is present and a QS complex is seen. At the age

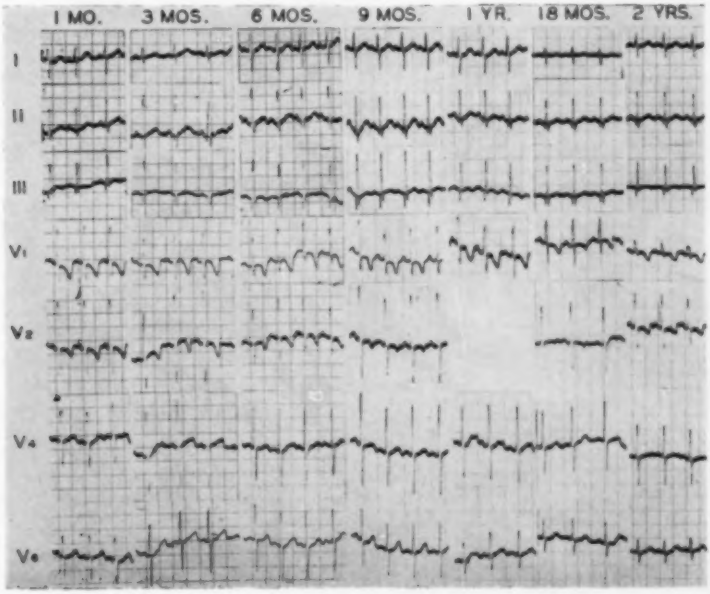

FIGURE 6: Serial electrocardiograms of an infant from one month to two years of age demonstrating the absence of any significant change during infancy.

of one month the R wave is usually higher and the S wave is less deep than at birth. During later infancy the R wave becomes even higher and the S wave becomes smaller and may disappear altogether. Sometimes, however, little change occurs after one month and an RS complex remains throughout infancy (Fig. 6).

Vectorcardiographic QRS Loops

The *frontal plane QRS loop of the tetrahedron* is virtually identical to the frontal plane loop of the Einthoven method and has previously been described in relation to the QRS complexes of the limb leads.

The *horizontal plane QRS loop of the tetrahedron* is usually inscribed clockwise in the newborn. A progressive change to a counterclockwise inscription of this loop usually occurs during infancy (Fig. 2). However, marked individual variation is encountered. We have observed loops which were inscribed counterclockwise in infants with marked right ventricular

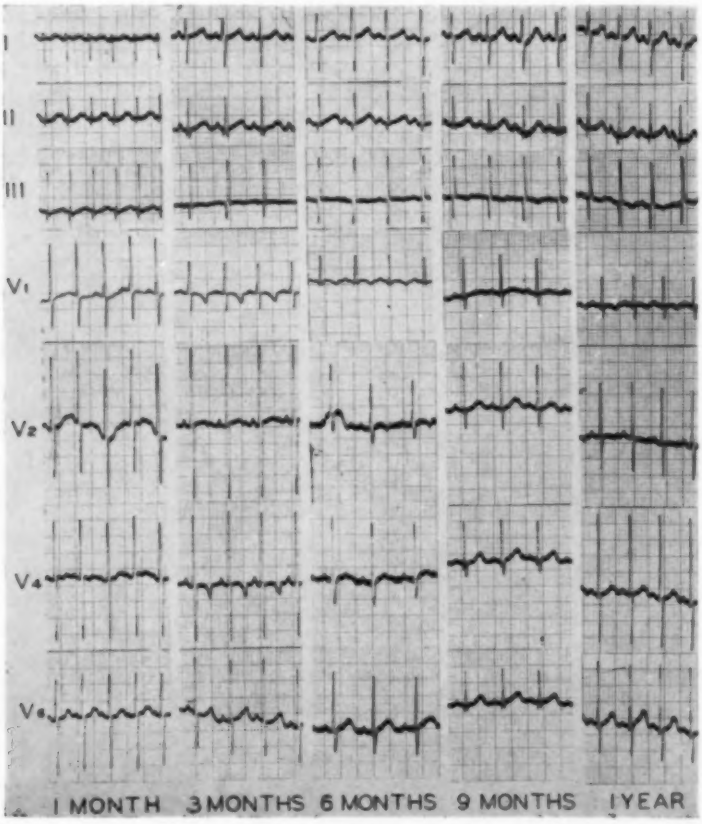

FIGURE 7: Electrocardiogram showing a Q wave in Lead V_1. This pattern in Lead V_1 is not rare among normal infants in the first year of life.

hypertrophy due to congenital heart disease and also loops which were inscribed clockwise in normal infants and even normal adults. In view of these observations and because of theoretical objections[5] to the back electrode of the tetrahedron we have not attempted a detailed analysis of the horizontal plane vectorcardiogram recorded with this frame of reference.

The frontal plane loop of the cube differs from that of the tetrahedron. It is generally oriented further to the left; it does not have the large terminal portion responsible for the large S waves in the standard limb leads; and it is narrower. It is also usually smaller than the frontal plane loop of the tetrahedron and it is more often inscribed in a counterclockwise manner.

In agreement with Stephen Elek[6] we have found that the *horizontal cube loop* in the newborn is usually inscribed clockwise and that during the first month of life it becomes a figure-of-eight with the centripetal limb passing well in front of the center point. After the first month or two the centripetal limb of the figure-of-eight loop passes either very slightly anterior to, through, or even posterior to the center point. Later the horizontal loop may be inscribed completely in a counterclockwise manner. Figure 2 illustrates the series of events seen in most infants. However, great individual variation is encountered. Figure 3 shows the electrocardiogram and vectorcardiogram of an infant on the first day of life and of another infant two years of age. Note that the horizontal loop of the former is inscribed counterclockwise and that of the latter is inscribed in a clockwise manner.

Effects of Respiration on the Electrocardiogram and Vectorcardiogram

The electrocardiographic and vectorcardiographic changes that occur during quiet breathing are more marked in infants than in adults. This phenomenon is most apparent in the right precordial leads and the horizontal plane loop of the cube.

In some infants the respiratory changes in the QRS complexes of Leads V4r and V1 are quite marked (Fig. 11). This is particularly evident when a distinct notch is present, for the latter may vary in its location from the ascending limb to the descending limb of the R wave or even into the S wave. Occasionally the notch becomes deeper resulting in an RSR' complex during one phase of respiration whereas in another phase the notch may not be noticeable. It is interesting that in spite of such pronounced changes in V1, little or no respiratory change may be noted in the other precordial leads or the extremity leads at the same time.

Respiratory variations are more evident in the vectorcardiograms than in the conventional leads because a change in the phase relationship of two leads is more rapidly discerned in the loops than when the two leads are viewed separately.

In several infants we have observed that during quiet respiration the horizontal loop of the tetrahedron or of the cube varies from the clockwise variety to the counterclockwise variety passing through a figure-of-eight stage between these (Figs. 12 and 13).

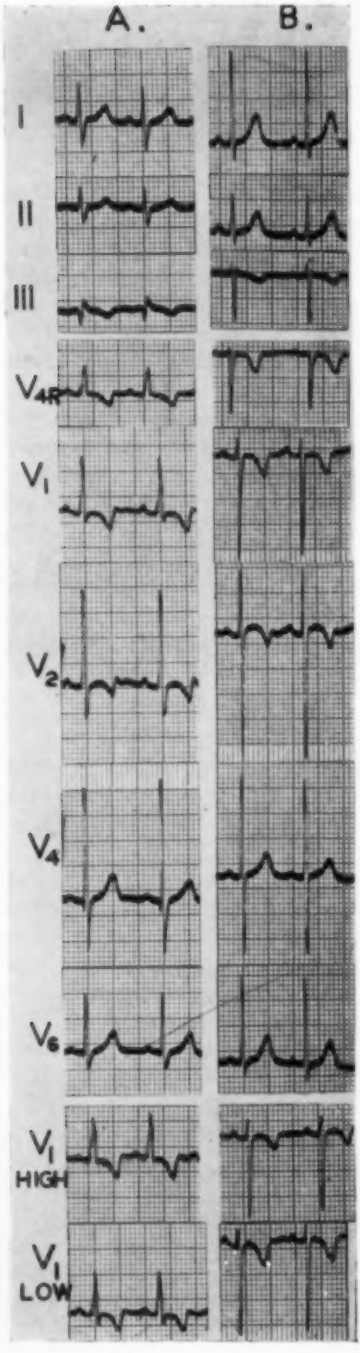

FIGURE 8: An illustration of the wide range of normal right precordial leads of two year old infants. V_{4R} and V_1 of A are not unlike that of a newborn infant whereas these leads in B are similar to that of an adult.

The T Wave

A complete discussion of the T wave should be based upon a more adequate knowledge of the process of repolarization of the ventricles of infants than is now available and should be concerned primarily with the ventricular gradient. Certain descriptive generalizations, however, can be made at this time.

The T wave in the limb leads, unlike the QRS complex, does not undergo any characteristic series of changes. We have not recorded electrocardiograms of infants less than twenty-four hours of age, but have noticed that the T wave of infants during the first month of life do not vary as much among individuals as does the QRS complex. In such infants the average mean frontal plane T wave axis (based upon the area of the T wave deflection) lies at about 45 degrees. The common pattern, therefore, is an upright T wave in Leads I and II and a small but upright T wave in Lead III. However, a flat or negative T wave in Lead III is not unusual. Although there are individual variations, the mean frontal plane T wave axis does

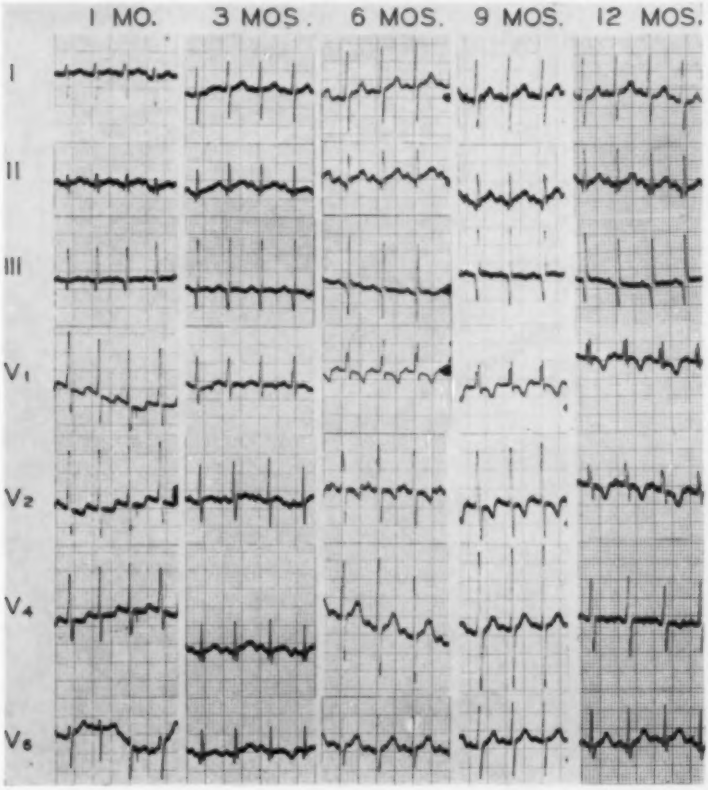

FIGURE 9: Serial electrocardiograms showing a progressive notching of the QRS complex in Lead V_1. At one month of age the R and S waves are of smooth contour. Evolution into an RSR'S' complex is seen.

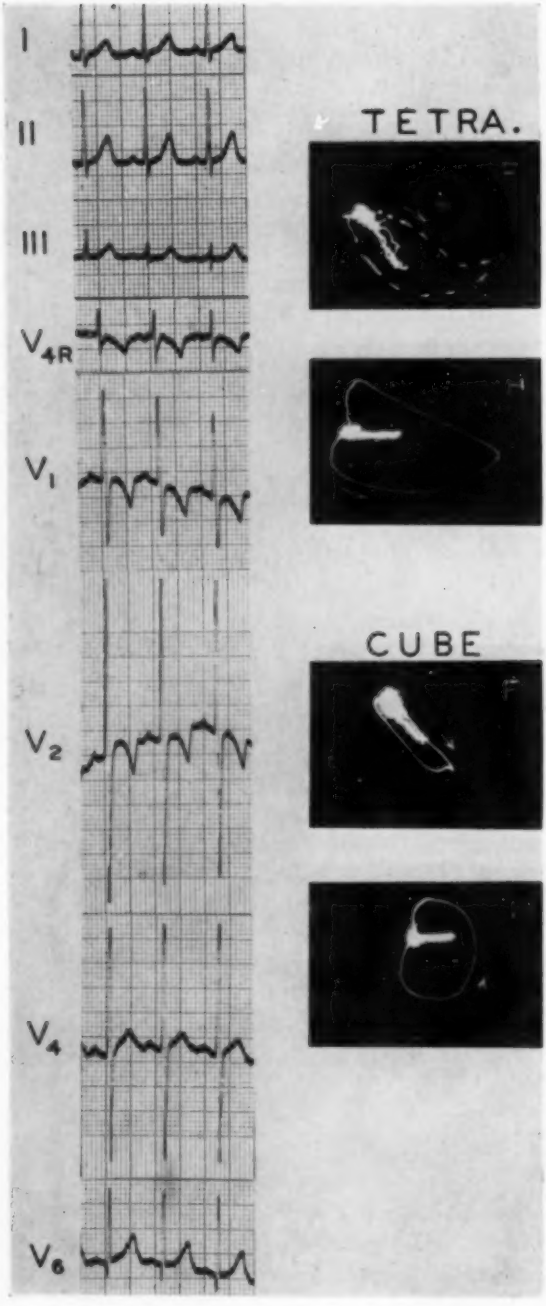

FIGURE 10: Electrocardiograms of a one year old infant demonstrating the large amplitude of the QRS complex that may be present in the precordial leads.

not change significantly in direction but usually increases in magnitude during the first three months. No further characteristic changes are seen in the limb leads during infancy.

During the first few days of life the T waves in Leads V4r and V1, especially the latter, are not infrequently upright. Characteristically the T waves in these leads become negative during the first few days of life (Fig. 2) and by the age of one month are deeply inverted. This is not invariably true and flat or even upright T waves are not rare at one month of age (Fig. 14). We have not observed a positive T wave in either V4r or V1 in normal infants three months of age or older. It is to be noted that diphasic — + or triphasic + — + T waves may be present in Lead V1 in normal infants over one month of age. In some of these infants, the T wave *area* in this lead is zero or slightly positive. When the T wave is upright in Lead V1 of one month old infants, the QRS complex in this lead most commonly consists of large R and S waves as seen in Figure 14B; less often it may be predominantly an R wave (Fig. 14A). We, therefore, cannot subscribe to the notion that positive T waves in the right precordial

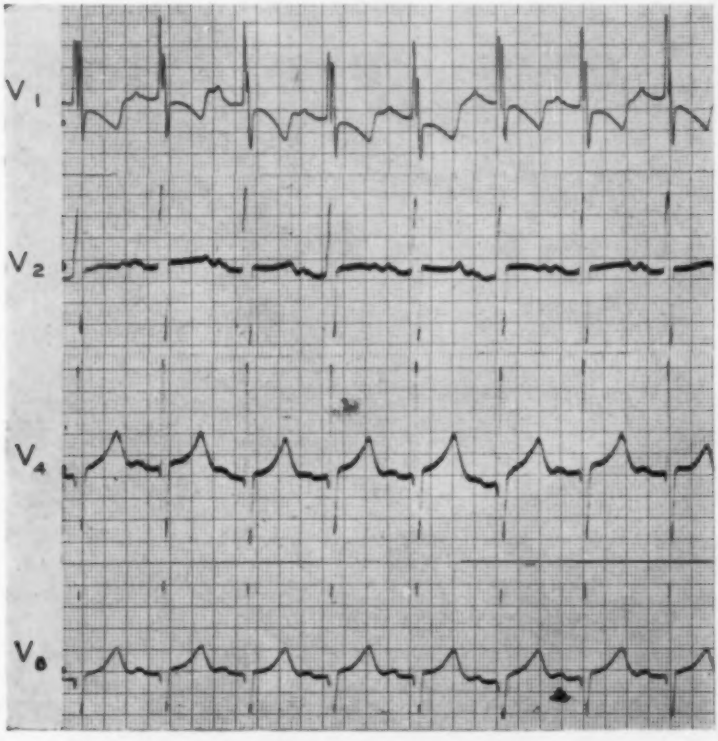

FIGURE 11: Simultaneously recorded precordial leads illustrating the marked respiratory changes that may occur in QRS complex in Lead V_1. Little or no respiratory variation is present in the other leads. (50 mm./sec. paper speed)

leads after the first twenty-four hours of postnatal life are highly suggestive, if not diagnostic, of pathologic right ventricular hypertrophy.[7]

In Leads V2 and V4, the T waves may be either upright or inverted. Inverted T waves are more common in V2 than in V4. An upright T wave may be present in V2 even when there is an inverted T wave in V4. No characteristic series of changes is usually seen in the T waves of these leads. Because of the critical location of the chest electrode of these leads, it is not uncommon to observe a change from a positive to a negative T wave in these leads, or vice versa, when repeated observations are made.

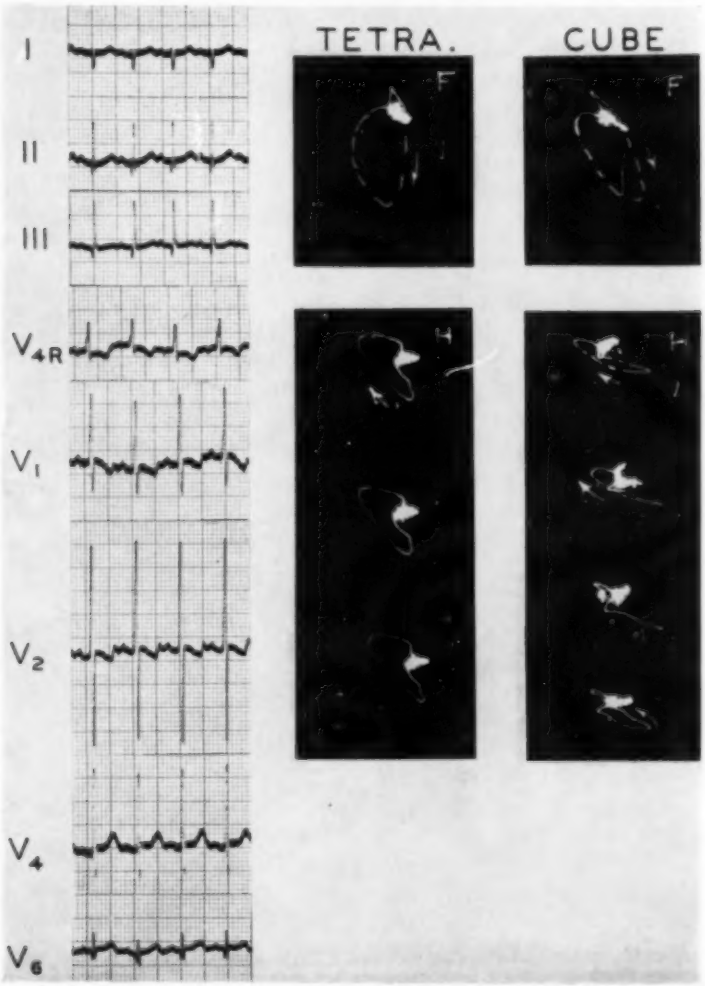

FIGURE 12: Electrocardiogram and vectorcardiogram of a one month old infant illustrating changes that occur during quiet respiration. Note that the horizontal loop of the cube varies with respiration from clockwise to a figure of eight inscription.

All of our tracings show upright T waves in V6 in early infancy. Inverted T waves in this lead may have been reported by others in infants less than twenty-four hours old. We have not made observations on infants this young. Frequently the T wave in this lead becomes greater in magnitude after the first few months of life. It may become inverted at very rapid rates when the QRS complex in this lead consists of a prominent R wave.

To properly evaluate the T wave of the electrocardiogram it is necessary to employ the concept of the ventricular gradient. In any case it is necessary to appreciate the fact that the T wave is very labile and depends for its form upon the QRS complex, the heart rate, and certain biochemical factors. Thus, a diagnosis of disease should not be based upon T wave changes which may be due to non-pathologic factors.[8, 9]

Discussion

The observations presented here reveal a progressive change in the electrocardiogram and vectorcardiogram throughout infancy, although the rate of progress of this change varies within extremely wide limits. Previously published observations of the various deflections of the electrocardiogram in normal infants have been found to be in error in a number of important respects: (1) The S wave in Lead I frequently disappears almost completely in the first few months of life; (2) the amplitude of R and S deflections in the precordial leads may be much greater than has been commonly reported. No definite limits of the normal can be established; (3) RS ratios in any lead are meaningless except when correlated with deflections of other leads.

The horizontal loop of the tetrahedron in infants behaves in such an irregular manner that it is valueless. The horizontal loop of the cube and the frontal plane loop of the tetrahedron show a progression of changes from birth to age two years although wide individual variation is encountered. Respiratory changes are common.

It is apparent that the persistence of high R waves in the right precordial leads, clockwise horizontal cube loops and other criteria employed by some in the diagnosis of right ventricular hypertrophy are frequently encountered in normal two year old infants.

Both practical and theoretic importance attaches to any correlation which might be found between the records of the cardiac potentials obtained by the employment of the various frames of reference presently in use. As stated previously the limb leads of the electrocardiogram and the frontal plane loop of the tetrahedron are recorded with the same frame of reference and present identical information. In early infancy large R waves in V4r and V1 are common as is right axis deviation but the correlation between right axis deviation and the amplitude and duration of the R waves in V4r and V1 in any one individual may not be good. Later in infancy it is even poorer. The descriptive correlation between the frontal plane QRS loop of the tetrahedron and the frontal plane QRS loop of the cube has been presented above.

Because clinical advantage has been claimed for the horizontal QRS loop of the cube[10] we have been especially interested in the possibility of correlating the conventional electrocardiographic leads with this loop. The progressive change which occurs through infancy in the limb leads (and therefore in the frontal plane QRS loop of the tetrahedron) only roughly parallels the corresponding changes in the horizontal loop of the cube. On the other hand, it is possible to correlate the electrocardiographic findings with the horizontal loop of the cube if, in addition to the limb leads, the right precordial leads V4r and V1 are employed. This correlation is shown in Figure 15. When marked right axis deviation (over 110 degrees) is present together with a large R wave and a small or no S wave in V4r and V1, the horizontal QRS loop of the cube is inscribed entirely in a clockwise manner (Fig. 15Aa). If marked right axis deviation is present and the amplitude and duration of R exceeds that of a well marked S in the right precordial leads the horizontal loop of the cube is inscribed largely clockwise but is narrow (Fig. 15Ab); a narrow figure-of-eight loop is seen if the R exceeds S in less degree than shown in complex b of Figure 14. If marked right axis deviation is present and the amplitude and duration of

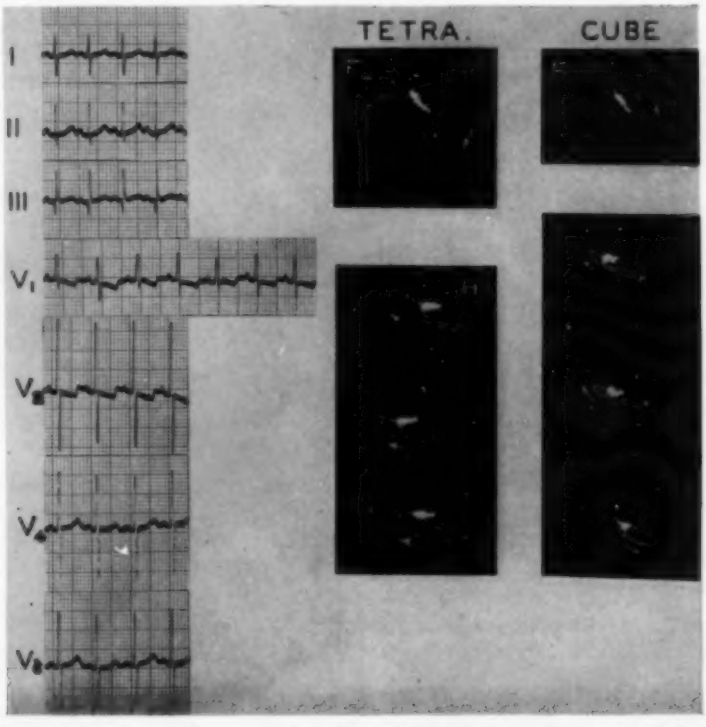

FIGURE 13: Electrocardiogram and vectorcardiogram of a one month old infant illustrating changes that occur during quiet respiration. These changes are most evident in Lead V_1 and the horizontal loop of the cube where the loop varies from clockwise to counter-clockwise inscription.

R and S are about equal in the right precordial leads, the horizontal QRS loop of the cube is of the figure-of-eight form with the centripetal limb passing anterior to the center point. A similar loop is inscribed when Lead I, V4r, and V1 all exhibit large R and S waves of equal amplitude and duration though the centripetal limb of the loop may pass through or just posterior to the center point in these cases (Fig. 15Bb). If, as occurs in some tracings, the deflections in Lead I are extremely small (narrow frontal loop of the tetrahedron lying on the 90 degree axis) or if there is

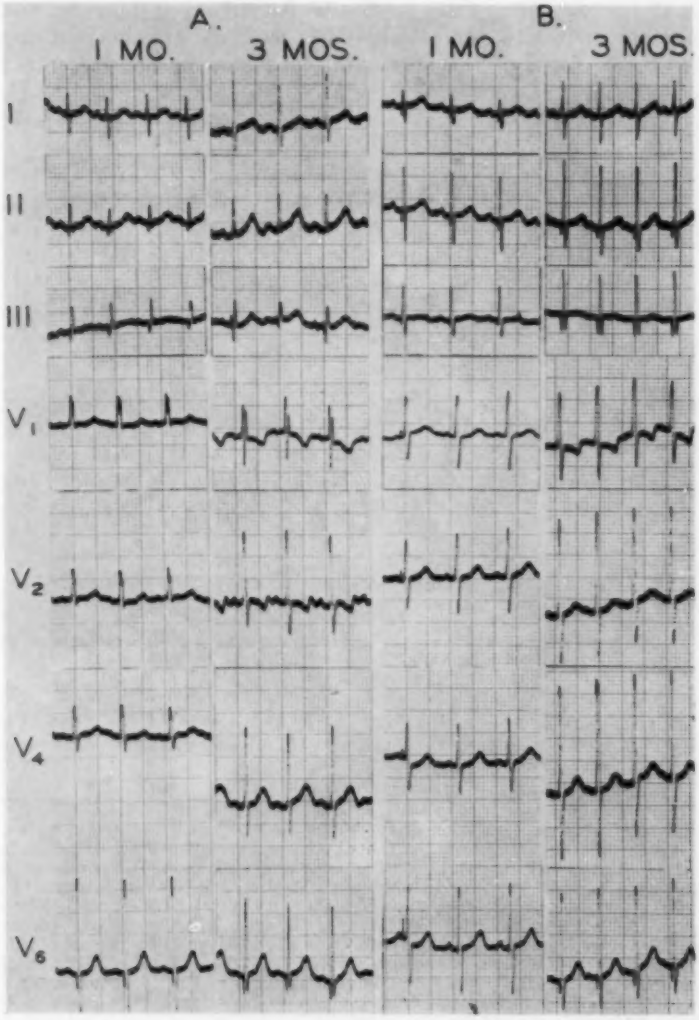

FIGURE 14: Electrocardiograms of two infants illustrating upright T waves in V_1 at one month of age and inversion at three months of age.

an R of moderate amplitude and little or no S in Lead I (frontal plane tetrahedron QRS loop directed to the left) and if R and S are of approximately equal magnitude in the right precordial leads then the horizontal loop of the cube is inscribed in a counterclockwise manner (Fig. 15Bc and Cc respectively). If under the latter conditions the R is of distinctly less magnitude than the S in V4r and V1, the horizontal loop of the cube approaches the adult form more closely. Other combinations of limb lead patterns and precordial lead findings and the corresponding horizontal cube loops are shown in Figure 15.

It is to be noted that right precordial leads having the RSR' configuration are not included in the table. It is more difficult but not impossible to predict the form of the horizontal cube loop in the presence of such complexes.

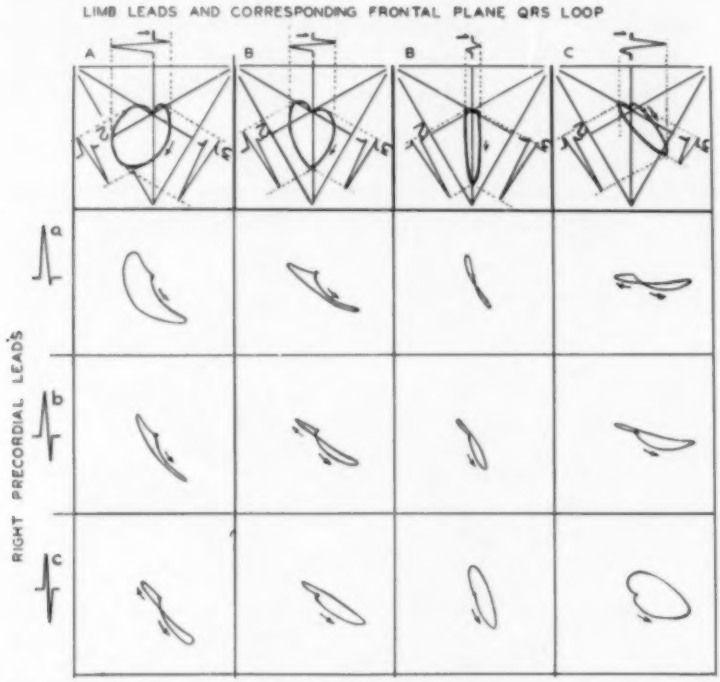

FIGURE 15: Table of correlation of the conventional electrocardiogram with the horizontal loop of the cube in normal infants. Across the top are the common limb lead patterns of infancy expressed also as frontal plane QRS loop. The extreme left hand column shows most of the forms of the right precordial leads (especially V_1) encountered in conjunction with the limb leads of the top row across. The table is used as is any other table. If the QRS in V_1 is as in *a* but *small* the corresponding loop is apt to be found in the horizontal row next below. It is to be noted that no right precordial lead is seen in the table which has the rsR' form (very small initial upward deflection, small S, and large final R'). This is omitted here because we encountered this finding but rarely among our normal infants thus far and therefore have little material for analysis. This may be due to the fact that we do not routinely make leads high on the right chest. This problem is to be attacked by the extension of this study into the area of congenital heart disease.

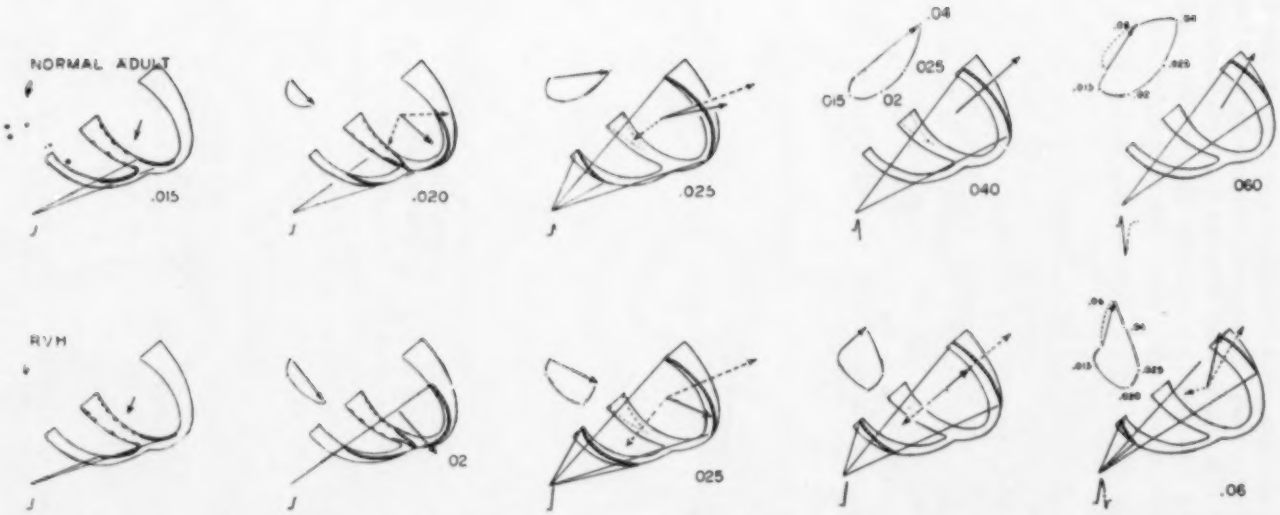

FIGURE 16: The physiologic basis of the QRS loop. Each diagram shows a longitudinal hemi-section of the ventricles of a transverse heart viewed from above so that the front of the chest is below and the back of the chest is above. The thick lines are the waves of excitation at the times (in seconds) indicated; these carry positive charges on their outer and negative charges on their inner surfaces. A vector is constructed for each wave of excitation. When two waves of excitation are present the parallelogram law is employed to determine the resultant. The succession resultant vectors draws the QRS loop (above each anatomic diagram). With the heart very transverse and non-rotated the spatial loop is the same as the "horizontal" loop were the latter recorded accurately. Comparison of the theoretic diagrams for the normal adult (a) with right ventricular hypertrophy (b) shows especially that 1) in the latter the 0.04 second vector is shortened greatly by the persistence of electrical effects in the right ventricular wall due to thickening of the latter. 2) the late vectors of the loop point more backward than in the normal.

It is to be thoroughly understood that the accurate prediction of the horizontal loop of the cube from the examination of the conventional electrocardiogram relates thus far only to the area which we have studied, the first two years of life. It is also to be understood that the correlation depends in no way upon any interpretation which has been or may be assigned to either the electrocardiographic or to the vectorcardiographic findings.

A Theoretic Approach to the Correlation of the Electrocardiogram with the Vectorcardiogram.

Whether one approaches the electrical phenomena of the newborn heart from the standpoint of leads or of loops recorded with any frame of reference it is apparent that the records are empirically those of right ventricular hypertrophy. It is equally apparent that a change toward the adult form takes place during the next few months and that there is much individual variation in the rate at which this change takes place. No very detailed study of the architecture of the heart from birth to late childhood is available but autopsy studies[11] show that at birth the ventricles

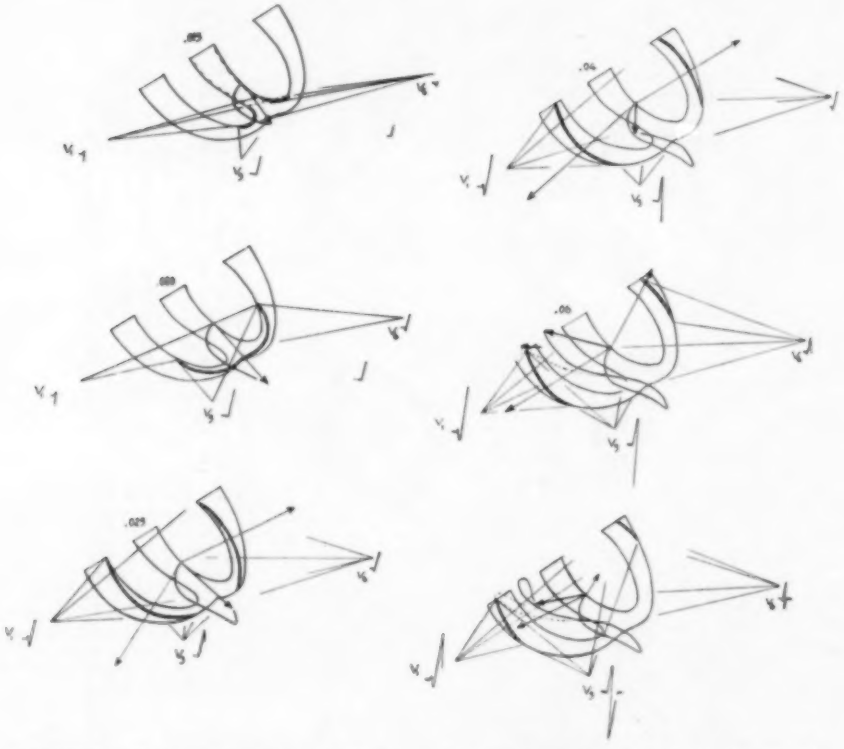

FIGURE 16C shows that were the horizontal loop recorded accurately a clockwise inscription of this loop cannot be expected unless the right ventricle is thicker than the left. In each diagram the deflections in V_1 are diagrammed employing the solid angle method.

are approximately of equal weight and that the left ventricle rapidly becomes larger and thicker while relative diminution in the size and thickness of the right ventricle occurs with little change in its weight. Although much individual variation is encountered, usually at the age of three months the relative size and thickness of the two ventricles is similar to that seen in adults.[11-12]

Most writers have continued to regard the electrocardiogram and the vectorcardiogram as empirical phenomena. In 1943 we presented an hypothesis of the progress of activation which made it possible to give meaning to the various portions of the normal adult QRS loop and to the corresponding portions of the deflections of the limb leads.[13] More recently, employing solid angle analysis we have extended application of the hypothesis to the precordial leads.[14] With this hypothesis as a basis it has been possible to make analyses of QRS loop and lead changes in a large number of pathological conditions.[14] It appears to us that an hypothesis which has been satisfactory for the explanation of a large number of electrocardiographic phenomena might be useful in the analysis of additional electrocardiographic problems. This notion is supported by the recent experimental corroboration of the major portion of this hypothesis by Scher,[15] Durrer[16] and Sodi-Pallares.[17]

We approached the present problem by employing the anatomic facts outlined above and the principles followed in the original hypothesis. We have diagrammed the events which one might expect to observe as a result of increasing the relative thickness of the right ventricle in Figure 16. Note that if the heart is non-rotated the spatial loop as shown in the diagram is roughly the horizontal loop for the more or less transverse heart of the infant.

In the normal adult (Fig. 16A) it is apparent that after the first 0.02 second the electrical effects of right and left ventricular activation are almost directly opposed to one another and that the long axis of the normal adult loop is almost perpendicular to the long axis of the heart because large left ventricular effects remain after activation in the right is virtually complete. It seems inescapable that we conclude that as the right ventricle becomes thicker it behaves more like the left ventricle; larger waves of excitation than those which occur in the normal adult must occur at corresponding times because of the increased thickness. Under these circumstances (Fig. 16B) the left ventricular effects are opposed more than in the normal adult and the longest vector of the loop (0.04 second) becomes shorter. In addition the later stages of excitation of the two ventricles produce vectors that are directed more posteriorly and that are larger than those which occur at corresponding times in the normal adult. When the two ventricles are of equal thickness the vectors would be directed first toward the apex and later toward the base as illustrated in Figure 16C. Only when the right ventricle is thicker than the left should the loop be inscribed in a clockwise manner.

It is immediately apparent that the horizontal loop of the cube is inscribed in a clockwise manner when the right ventricle is not as thick as

the left in cases of right ventricular hypertrophy associated with certain congenital lesions and in normal infants. Even at birth the right ventricle is usually not thicker than the left, and it certainly is not at two months. Were the loop recorded *accurately* (without distortion) clockwise rotation of the heart would not explain such loops as are recorded under the circumstance under discussion. The inference which must be drawn is that the clockwise inscription of the horizontal loop of the cube in early infancy and in moderate right ventricular hypertrophy is in all likelihood the result of *distortion inherent in the method of recording*. The phenomenon is analagous to the exaggeration of the degree of electrical rotation which results from eccentricity when the Einthoven method is employed. The extent of this distortion may be expected to vary from individual to individual and in the same individual with alteration of the relation of the heart to the chest wall. This inference is supported by the observation of a respiratory effect upon the horizontal loop of the cube during normal breathing in many infants (Figs. 12-13). If this variation is due to rotation it is obvious that the rotation is exaggerated. We cannot subscribe to the notion that the left ventricle ever faces anteriorly in these infants. If normal respiration can change a clockwise loop to a counterclockwise one it seems inescapable that individual variations in thoracic contour can accomplish the same phenomenon.

The conclusion is reached that the *horizontal loop of the cube exaggerates the right ventricular effects*. The fact that the right precordial leads contain a like "error" accounts in large part for the finding that it is possible to predict the form of the horizontal loop of the cube from examination of the conventional electrocardiogram. The contribution which the limb leads make to this correlation is due to the exaggeration of clockwise rotation by the eccentricity effects when the Einthoven method is used.

Our remarks upon this area of electrocardiography and vectorcardiography are not intended to disparage either the one method or the other, though we do deplore the use of the back electrode of the tetrahedron. Those of us who for many years have been accustomed to viewing limb leads as projections of a spatial QRS loop which we construct from these leads and partially by inference have been employing the concept of the vectorcardiogram as a basis for our thinking without the benefit of the oscilloscope which constructs loops automatically. It is not difficult for us to understand that there are many who were accustomed to view leads individually and who first came in contact with loops through the oscilloscope. Because of this difference in discipline the latter group may find certain changes more easily in loops than in leads while to us the same phenomena may be just as evident in the leads. Actually each method has advantages and disadvantages. Timing in vectorcardiograms is poorer than in electrocardiograms but phase relationships are vastly more superior in vectorcardiograms. Caution should be exercised before concluding that one method is superior to the other in relation to any clinical problem. It is possible that the accurate phase relationship of the oscilloscopic records will be of more value in some areas of electrocardiographic inter-

pretations. It also seems possible (other opinions to the contrary notwithstanding) that the precordial leads will remain more valuable for some purposes than will vectorcardiograms.

SUMMARY

1. Electrocardiograms and vectorcardiograms (both the cube and tetrahedron frames of reference) were recorded on 300 infants one to 30 days of age. These infants were restudied at intervals of one to three months during the first year and every six months thereafter. Many have now reached the age of two and one-half years.

2. Considerable variation was found in the electrocardiogram among individuals. Most commonly there was a gradual change in direction of the mean QRS axis toward the left during infancy, but right axis deviation (110° to 120°) sometimes persisted throughout infancy. The development of left axis deviation after three months of age was not rare. The large R wave in Leads V4r and V1 may remain throughout infancy, but more commonly, gradually become smaller. Notching of the R wave in these leads were not seen in newborns but was not infrequent later. Small Q waves in these leads were not rare. Extremely high voltage may be seen in the chest leads, especially V2 and V4.

3. Correlation exists between the standard electrocardiogram and vectorcardiogram. The frontal plane QRS loop of the tetrahedron contains virtually identical information as the standard Einthoven leads; the horizontal plane loop of this system was found to be valueless. The horizontal loop of the cube *usually* was inscribed clockwise in newborns, later it became a figure-of-eight, and finally an open loop inscribed in a counterclockwise manner. Great individual variation was encountered: a counterclockwise loop may be seen in newborns and a clockwise loop in two year olds. The horizontal loop of the cube system could be predicted from the standard electrocardiogram fairly accurately.

4. The T waves of the limb leads do not differ among individuals as much as the QRS complexes nor do characteristic serial changes occur. During the first few days of life the T wave in Leads V4r and V1 is not infrequently upright, but this is uncommon at one month and was not seen by three months of age.

5. A theoretical analysis of the QRS loop of the infant, based on anatomical and physiological data, is presented. Theoretically the horizontal projection of the QRS loop would not be expected to be inscribed in a clockwise manner unless the right ventricle was thicker than the left. Since this is not true even during the first few months of life, it is believed that a distortion inherent in the cube system of vectorcardiography exaggerates the right ventricular effects to produce the clockwise inscribed loops seen in records made with this method.

RESUMEN

1. Se hicieron electrocardiogramas y vectocardiogramas (ambos el cubo y tetraedro como cuadros de referencia), en 300 infantes de uno a 30 días

de nacidos. Estos infantes fueron vueltos a estudiar a intervalos de uno a tres meses durante el primer año de vida y después cada seis meses. Muchos han alcanzado ahora la edad de dos y medioaños.

2. Se encontró considerable variación entre los electrocardiogramas individuales. Lo más común es que haya un cambio gradual en la dirección del eje de QRS hacia la izquierda en la infancia, pero la desviación del eje a la derecha (110° a 120°) a veces persistió através de toda la infancia. El desarrollo de desviación del eje a la izquierda después de tres meses de edad, no fué rara.

La R amplia en V4r y V1 puede permanecer a través de toda la primera infancia pero más a menudo se hace menor. La muesca de la onda R en estas derivaciones no se vió en los reciennadicos, pero no infrecuente más tarde. Un voltaje extremadamente alto puede verse en las derivaciones del pecho, especialmente V2 y V4.

3. Existe correlación entre el ECG estandar y en vectocardiograma. El gancho del plano frontal QRS del tetraedro contiene virtualmente información idéntica que las derivaciones estandar de Einthoven; el gancho del plano horizontal de este sistema se encontró sin valor. El gancho horizontal del cubo, generalmente se inscribió en el sentido de manecilla de reloj en los reciennacidos, más tarde se convirtió en figura de ocho y finalmente en un gancho abierto inscrito en sentido contrario a las manecillas. Grandes variaciones individuales se encontraron: un gancho en sentido contrario a las manecillas de reloj puede observarse en reciennacidos y en el sentido de las manecillas en los de dos años. El gancho horizontal del sistema del cubo podría predecirse a partir del ECG estandar, con bastante precisión.

4. Las ondas T de las derivaciones de los miembros inferiores no difieren entre individuos tanto como los complejos QRS ni hay cambios característicos en series. Durante los primeros días de la vida la onda T en las derivaciones V4r y V1 no es raramente recta, pero esto es poco común al mes de vida y no se vió a los tres meses.

5. Un análisis teórico del gancho QRS en el infante, basado en datos anatómicos y fisiológicos se presenta. Teóricamente la proyección horizontal del gancho QRS no es de esperarse que se inscriba en el sentido de las manecillas a menos que el ventrículo derecho sea más grueso que el izquierdo. Puesto que esto no es observado aún durante los primeros meses de vida se cree que una distorsión inherente al sistema del cubo de la vectocardiografía exagera el efecto ventricular izquierdo para producir los ganchos inscritos en sentido de la manecilla como se ven en los récords inscritos con este método.

RESUME

1. Les électrocardiogrammes et vectocardiogrammes (enregistrés à l'aide des systèmes de référence à la fois cubique et tétrahédrique) furent enregistrés chez 300 jeunes enfants âgés de 1 à 30 jours. Ces enfants furent observés de nouveau à des intervalles de 1 â 3 mois pendant la pre-

mière année, et tous les six mois ensuite. Plusiers ont maintenant atteint l'âge de 2 ans et demi.

2. On trouva une variation considérable dans les électrocardiogrammes selon les individus. Le plus souvent, il y eut un changement progressif de la direction de l'axe moyen de QRS vers la gauche, durant la première enfance, mais la déviation vers la droite (110° ou 120°) a persisté quelquefois pendant l'enfance. Le développement de la déviation vers la gauche après l'âge de trois mois n'est pas rare. La grande onde R dans les dérivations V4r et V1 peut subsister pendant l'enfance, mais plus souvent, devient progressivement plus petite. On ne constata pas de crochetage de l'onde R dans ces dérivations chez les nouveaux-nés, mais ce phénomène ne fut pas rare par la suite. De petites ondes Q dans ces dérivations ne sont pas rares. On peut voir des voltages extrêmement élevés dans les dérivations thoraciques, particulièrement en V2 et V4.

3. Une corrélation existe entra l'électrocardiogramme standard et le vectocardiogramme. La boucle frontale plane QRS du tétrahèdre contient virtuellement des renseignements identiques à ceux des dérivations standard d'Einthoven: la boucle horizontale plane de ce système s'est montrée sans valeur. La bouche horizontale du cube est *habituellement* inscrite dans le sens horaire chez les nouveaux-nés, ensuite elle prend une forme de huit, et finalement celle d'une boucle ouverte inscrite dans le sens antihoraire. On rencontre des variations selon l'individu: une boucle antihoraire peut être vue chez les nouveaux-nés et une boucle horaire chez les enfants âgés de deux ans. La bouche horizontale du système cubique est prévue avec assez de précision d'après l'électrocardiogramme standard.

4. Les ondes en T des dérivations des membres ne différent pas suivant les individus autant que less complexes QRS et l'on n'observe pas de modifications caractéristiques successives. Pendant les premiers jours de la naissance, l'onde T dans les dérivations V4r et V1 n'est pas rarement positive, mais ceci est rare á un mois et n'a pas été noté après trois mois.

5. L'auteur présents une analyse théorique de la boucle QRS chez le bébé, basée sur les données anatomiques et physiologiques. Théoriquement, on ne s'attendait pas à ce que la projection horizontale de la boucle QRS s'inscrivît d'une manière horaire, à moins que le ventricule droit ne soit plus épais que le gauche. Puisque ceci n'est past exact, même pour les quelques premiers mois de la naissance, on peut estimer qu'une distorsion inhérente au système cubique de la vectocardiographie exagère les effets ventriculaires droits pour produire les boucles inscrites dans le sens horaire qui sont notées dans les enregistrements faits selon ce procédé.

ZUSAMMENFASSUNG

1. Electrocardiogramme und Vectorcardiogramme (sowohl die wesentlichen Würfel- als auch die Tetraeder-Form) wurden von 300 Kindern im Alter von 1-30 Tagen aufgenommen. Diese Kinder wurden dann wieder untersucht in Intervallen von 1-3 Monaten während des ersten Jahres und alle 6 Monate danach. Viele haben jetzt ein Alter von 2½ Jahren erreicht.

2. Es wurden beträchtliche Variationen gefunden im Electrocardiogramm unter den einzelnen Fällen. Am häufigsten ergab sich ein allmählicher Wandel in der Richtung der Haupt- QRS-Achse nach links während der frühen Kindheit; aber mitunter blieben rechtsseitige Abweichungen der Achse (110°-120°) durch das Kleinkindesalter bestehen. Die Entwicklung der Linksachsigen Abweichung jenseits eines 3-monatigen Alters war nicht selten. Die hohe R-Zacke in Ableitung V4r und V1 können durch das frühe Kindesalter erhalten bleiben, aber für gewöhnlich werden sie allmählich niedriger. Knotung der R-Zacke in diesen Ableitungen fand sich nicht bei Neugeborenen, war aber später nicht selten. Niedrige Q-Zacken in diesen Ableitungen waren nicht selten. Extreme Hoch-Voltage kann in den Brustkorbableitungen, besonders V 2 und V 4 vorkommen.

3. Es besteht eine Korrelation zwischen dem Standard-Electrocardiogramm und dem Vectorcardiogramm. Der QRS-Komplex der frontalen Ebene des Tetraeders enthält tatsächlich mit dem Standard-Einthoven-Ableitungen identische Informationen; der Komplex dieses Systems in der horizontalen Ebene erwies sich als wertlos. Die horizontale Schleife des Kubus verlief bei Neugeborenen für gewöhnlich im Sinne des Uhrzeigers, später wurde daraus die Figur einer Acht und schliesslich eine offene Schleife mit Verlauf in dem Uhrzeiger entgegen gesetzten Sinn. Erhebliche individuelle Abweichgen wurden festgestellt: eine Schleife entgegen dem Uhrzeiger kann bi Neugeborenen zu sehen sein und eine Schleife mit Uhrzeigermässigem Verlauf bei Zweijährigen. Die horizontale Schliefe des kubischen Systems lässt sich ziemlich genau aus dem Standard-Electrocardiogramm voraussagen.

4. Die T-Zacken der Extremitäten-Ableitungen weichen im Einzelfall nicht so stark voneinander ab wie die QRS-Komplexe, und es treten eben so wenig periodische Änderungen auf. Während der allerersten Lebenstage verläuft die T-Zacke in den Ableitungen V 4r und V 1 nicht selten aufrecht, aber dies ist bereits im Alter von einem Monat ungewöhnlich und mit drei Monaten nicht zu sehen.

5. Es wird eine theoretische Analyse des QRS-Komplexes beim Kleinkind vorgelegt, die von anatomischen und physiologischen Grundlagen ausgeht. Theoretisch müsste man nicht erwarten, dass die horizontale Projektion des QRS-Komplexes im Sinne des Uhrzeigers abläuft, ausser der rechte Ventricel wäre stärker als der linke. Da dies aber nicht einmal zutrifft für die allerersten Lebensmonate, wird angenommen, dass ein dem kubischen System der Vectorcardiographie innewohnende Dystorsion, die Effekte des rechten Ventricels steigert zu Abläufen der Schleifen im Sinne des Uhrzeigers, wie sie bei den mit dieser Methode erhobenen Befunden zu sehen sind.

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Clinical Experience with Terramycin* as an Adjunctive Agent in the Chemotherapy of Tuberculosis

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An impressive volume of data on the chemotherapy of tuberculosis has been provided by the fifteen conferences sponsored since 1946 as a continuing cooperative project of the Veterans Administration, the Army, and the Navy. More than 50 hospitals have presented reports on some 20,000 patients, and three drug combinations have been established as basic regimens of about equal efficacy—streptomycin plus para-aminosalicylic acid, isoniazid plus para-aminosalicylic acid, and streptomycin plus isoniazid.

The three drugs in these combinations are the agents in most general use; but others in occasional use, for special indications, include viomycin, oxytetracycline (Terramycin), and most recently cycloserine. Particular emphasis must be placed on the use of combinations in the treatment of tuberculosis in order to prevent or delay the emergence of resistant bacilli. Protection against the early appearance of resistant organisms by genetic mutation is of primary concern, for successful therapy depends upon the continuing efficacy of the drugs over a period of some two years or even longer.

The utility of the less commonly used agents (viomycin, Terramycin, and cycloserine) arises from the need for longer-term therapy in patients whose bacilli have become insensitive to at least two of the three basic drugs (streptomycin, isoniazid, and para-aminosalicylic acid), for even their use in combination fails to protect against this eventuality in cases requiring especially prolonged therapy. Although the three basic combinations differ little in efficacy, some disadvantage is seen in the use of streptomycin and isoniazid together—as these are the two most effective drugs, and their use together risks the possibility of the emergence of resistance to both at the same time, leaving no weapon of comparable efficacy with which to carry on further therapy. It would seem preferable to start with either isoniazid plus para-aminosalicylic acid or streptomycin plus para-aminosalicylic acid.

Isoniazid plus para-aminosalicylic acid is now the combination most often chosen, since both drugs can be given by mouth—300 mg. of isoniazid daily, in divided doses, and 12 Gm. of para-aminosalicylic acid daily, in divided doses. When the disease is acute, with extensive cavitation and caseation, first choice is *daily* administration of streptomycin (1 Gm. and para-aminosalicylic acid. When streptomycin is used in the treatment of nonacute disease, it is administered twice weekly (1-Gm. doses).

*Terramycin for this study was supplied by Dr. M. William Amster, Medical Department, Pfizer Laboratories, Brooklyn 6, New York.
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Some patients prove so intolerant of para-aminosalicylic acid that another agent must be substituted. It is in this role that Terramycin finds usefulness in the chemotherapy of tuberculosis. In combination with streptomycin therapy, Terramycin (1 Gm. daily in divided doses) has been found as effective as para-aminosalicylic acid in limiting the rate of emergence of resistant strains.[1, 2]

Data are still needed concerning the efficacy of a combination of isoniazid and Terramycin, and the principle purpose of the study here reported was to contribute toward this need. Replacement of para-aminosalicylic acid with a similarly effective minor agent to be used in conjunction with the major agent (streptomycin or isoniazid) is frequently necessary because of intolerance of para-aminosalicylic acid in therapeutic dosage (12 Gm. daily divided doses). Intolerance is manifested in such disturbing reactions as epigastric discomfort, anorexia, nausea and vomiting, and occasionally diarrhea. When isoniazid is to be used as the major drug in such cases, as well as in the fairly large number of patients whose tubercle bacilli have become resistant to both streptomycin and para-aminosalicylic acid during successive courses over several years, the use of isoniazid alone (or in combination with para-aminosalicylic acid if organisms are no longer sensitive to this latter agent) would carry great risk of prompt emergence of strains resistant to isoniazid. For these patients, a combination of isoniazid and some other antituberculosis drug to which tubercle bacilli are still sensitive is required.

Clinical Experience

Although small-scale studies of several other applications of Terramycin are included in the following account, its principal import is in its report of a study of Terramycin used as an adjunct to isoniazid, which suggests that this combination, like the combination of Terramycin and streptomycin, offers an entirely satisfactory solution to the problem of preserving sensitivity to the major agent. In either combination, 1 Gm. of Terramycin daily (in divided doses) appears equal in effectiveness to para-aminosalicylic acid (12 Gm. daily in divided doses).

Terramycin Used as an Adjunct to Streptomycin

Only one patient in the experience here reported received the combination of streptomycin and Terramycin. This one was unable to tolerate para-aminosalicylic acid.

Case 1: This 74-year-old man was admitted to the hospital in April, 1955, with advanced bilateral silicotuberculosis and in almost critical condition. As he proved unable to tolerate para-aminosalicylic acid, he was treated for five months with streptomycin and isoniazid. After this period of continuous therapy peripheral neuritis developed. This appeared to be a reaction to isoniazid, and a change was therefore made to a combination of streptomycin (1 Gm. twice a week) and Terramycin (1 Gm. daily in divided doses). He has continued on this combination for over a year. Although his sputum remains positive, the clearing of both lungs has been remarkable and the general improvement in his clinical condition has been most gratifying.

Terramycin Used as an Adjunct to Isoniazid

We now arrive at the observations that are the special warrant for this report—experience with the combination of isoniazid and Terramycin in the treatment of 16 patients with advanced pulmonary tuberculosis.

Case 2: This 49-year-old woman was admitted in September 1953 with far-advanced pulmonary tuberculosis involving the entire right lung. There was a huge cavity in the right upper lobe and lesser infiltration in the midfield on the left. The combination of streptomycin and para-aminosalicylic acid was used for about 18 months. Isoniazid was administered in addition for a portion of this period. After this time, however, streptomycin could no longer be tolerated and it was with the combination of isoniazid and Terramycin that therapy was continued. After six months on the new therapy she had continued to show improvement and it was thought that radical surgery could reasonably be contemplated. Therapy was at this time changed back to the combination of streptomycin and isoniazid, and a month later first-stage thoracoplasty was performed; this was followed after another month with a successful second-stage thoracoplasty. She was continued on the streptomycin-isoniazid combination, and three months after the second operation sputum-conversion appeared to have been effected. The sputum has remained negative on repeated tests ever since. During the past year she has continued on streptomycin-isoniazid at home. In this case Terramycin served a vital need during the crucial time that streptomycin could not be used—a time when it was necessary to continue some effective drug action to prepare the patient for surgery.

Case 3: This 33-year-old woman was admitted in March 1952 with far-advanced bilateral pulmonary tuberculosis—with extensive thoracoplasty on the right hydropneumothorax in the operative side, and contralateral lesions. With streptomycin plus para-aminosalicylic acid no improvement was observed, and after three years of therapy with this combination she became unable to tolerate streptomycin. A change was made to isoniazid plus Terramycin, and this combination appeared at least as effective as the previous therapy—that is, there was no apparent progression. After nine months on the new combination she died from complicating conditions. The use of Terramycin had served well, both for its holding action against progression of the tuberculous lesions and for its protection against possible secondary nontuberculous infections. She was unfortunately beyond additional surgical treatment, however, and Terramycin could of course not be expected to produce greater benefits than streptomycin.

Case 4: This 31-year-old man was admitted first in 1945, again in 1948, and for the third time in 1950. He had already, by the time of this third hospitalization, had an extensive three-stage thoracoplasty on the left side, with a small extrapleural pack in the right upper lobe (there was also a small patchy area of infiltration in the right lower lobe, but this was quite well constricted)—and over the preceding years he had received extensive courses of streptomycin to which para-aminosalicylic acid had been more recently added. After his third admission, in 1950, he was continued for four years on a combination of streptomycin and isoniazid; but he then could tolerate streptomycin no longer. His sputum had become alternatingly positive and negative (as it has remained since). Bronchography showed remaining bronchiectatic areas in the operative side—these were (and are) probably maintaining the positive sputum. Revision pneumonectomy on the left has remained impracticable because of his low vital capacity—and even lower spirits. After development of intolerance to streptomycin, treatment was continued with isoniazid in combination with Terramycin for six months. It was then possible to resume the streptomycin-isoniazid combination, and it is hoped that the progression of improvement will not be further complicated to delay the advisable pneumonectomy on the left side.

Case 5: This 39-year-old man had diabetes as well as far-advanced tuberculous involvement throughout the entire left side (a huge cavity occupying almost the entire left side) and the upper half on the right side. He was admitted to the hospital with these findings in August 1951, and from that time until three years later his treatment included a diabetic diet, insulin, and the combination of streptomycin plus isoniazid. After three years, the development of allergic dermatitis caused the discontinuation of streptomycin, and Terramycin was then added to the continued isoniazid therapy. This new combination, together with therapeutic pneumoperitoneum, was employed for eight months, with no lesser benefit than had been realized with previous therapy. As he, by the end of this period on isoniazid plus Terramycin, appeared to be approaching readiness for surgical treatment, a change was made back to the streptomycin-isoniazid combination (with para-aminosalicylic acid also) for a month, and a first-stage thoracoplasty was then performed. The triple drug combination was continued, a second-stage thoracoplasty was performed a month after the first procedure, and now, although continuation of the drugs, during the several months since the second operation, has not yet succeeded in producing sputum-conversion, he is doing exceptionally well clinically.

Case 6: This 74-year-old woman was admitted to the sanatorium in December 1951 with bilateral upper lobe lesions and with cavitation in the right upper lobe. After

three years of streptomycin in combination with para-aminosalicylic acid, the occurrence of dizziness made the discontinuation of streptomycin advisable. Isoniazid in combination with Terramycin was then instituted, and this has been continued for over a year. She continues to show clinical improvement, and the present combination is judged at least equal to the earlier one. Her sputum remains positive, however, despite evidence of clinical improvement.

Case 7: This 45-year-old man was admitted first in August 1951 with far advanced bilateral lesions and in a critical condition. The more extensive involvement was on the right side, where there was a huge cavitation. Treatment included streptomycin plus para-aminosalicylic acid as well as therapeutic pneumoperitoneum and right phrenic nerve crush. Development of exfoliative dermatitis after a year's treatment, however, prevented further use of streptomycin. He then left the sanatorium, and another year passed before he was readmitted. Streptomycin was again tried, but again it produced severe allergic reactions. Furthermore, para-aminosalicylic acid was not tolerated now because of gastric distress. The combination of isoniazid and Terramycin was administered for eight months, when he was discharged for disciplinary reasons. Improvement with this combination was most gratifying. The lesions continued to clear until, at the time of discharge, he had almost complete resolution on the left side and only a fine fibrotic infiltration in the right upper lobe. A thin-walled cavity persisted in this fibrotic area, however, and positive sputum persisted. The therapy had reduced the disease so surgery was indicated for the residual lesions, however— a notable achievement in a patient able to tolerate only one of the principal antituberculosis drugs, for emergence of resistant strains to that drug if it were used alone would have prevented the successful outcome that the addition of Terramycin was instrumental in achieving.

Case 8: This 54-year-old woman had a history of many years of sanatorium care. She came for treatment in July 1955 with negative sputum but with extensive, constricted, and honeycombed lesions throughout the entire left side. She had been on streptomycin before admission and gave a history of being allergic to it. She also had difficulty in tolerating para-aminosalicylic acid. Pneumonectomy on the left side had been attempted before she was admitted here but had been discontinued for technical reasons. On isoniazid and Terramycin, she has done exceptionally well. Clearing and constriction has taken place in the left side, and we are preparing her for thoracoplasty.

Case 9: This 47-year-old man was admitted in October 1954 with advanced disease including cavitation throughout both lungs. Pneumoperitoneum could not be used on account of hernia. After streptomycin and para-aminosalicylic acid, for a year, severe headaches followed streptomycin injections. Drugs were changed to isoniazid and Terramycin. Except for two temporary relapses, one caused by overdoing during a leave of absence, the other by left spontaneous pneumothorax, he showed a most remarkable clearing throughout both lung fields. After four months, however, he left on his own accord, with sputum still positive. The isoniazid and Terramycin combination was as effective as the previous combination.

Case 10: This man was admitted in October 1955 with far-advanced disease of the right lung. Streptomycin and isoniazid, pneumoperitoneum and right phrenic nerve crush did not result in remarkable clearing of the lesions. After four months, numbness and impaired hearing developed. Isoniazid and Terramycin were substituted. He did as well on this as on the previous combination but had to be discharged for disciplinary reasons after only two months.

Case 11: This 61-year-old man had advanced disease of the right lung. PAS not being tolerated, he was started on streptomycin and isoniazid. Intolerance to streptomycin developed and Terramycin was substituted. He did exceptionally well, but died six months later from coronary disease.

Case 12: This 33-year-old man with severe deforming arthritis was admitted in May, 1947 with advanced bilateral pulmonary tuberculosis. He received several courses of streptomycin with para-aminosalicylic acid or isoniazid, or with both, during the next eight years. Streptomycin then caused symptoms, and he was put on isoniazid and Terramycin. His lung picture has not changed during a year on this combination but there was slight clinical improvement—the first during all the years on treatment.

Case 13: This 49-year-old man was admitted in June, 1951 with moderately advanced pulmonary tuberculosis, with cavitation of the right upper lobe. He was given streptomycin with either para-aminosalicylic acid or isoniazid or both, over a period of three years. He left but returned nine months later, still with positive sputum and receiving the same drugs. He was then given isoniazid, Terramycin and para-aminosalicylic acid, but Terramycin was discontinued in one month, at his request, for which he

gave no explanation. During the subsequent year, isoniazid and para-aminosalicylic acid have been continued but he has refused surgery. During the short period Terramycin was used he did at least as well as before or after.

Case 14: This 67-year-old man was admitted in June, 1947 with extensive fine patchy lesions through the entire right and part of the left lung. During the following eight years he received extensive courses of streptomycin, in combination with isoniazid during the latter half of this period. He had shown but little improvement. All antituberculosis medication was then stopped, because of hepatitis. Four months later isoniazid and Terramycin were started. He did well but after two months he requested that streptomycin be substituted for Terramycin. He did as well on isoniazid and Terramycin as on any of the previous or subsequent drug combinations.

Case 15: This 32-year-old man had advanced cavitary disease in the upper lobe of the right lung. He did quite well on streptomycin with para-aminosalicylic acid or isoniazid or both, but marked soreness resulted from the streptomycin injections and he was therefore changed to isoniazid and Terramycin. He continued to do well but after one month he requested streptomycin instead of Terramycin, for no apparent reason.

Case 16: This 68-year-old man with silicotuberculosis, only moderately active, was admitted in July, 1955. He was treated for a year with streptomycin and isoniazid when dizziness and difficulty of hearing developed, streptomycin was replaced with Terramycin. His complaints disappeared quickly and after only a month on the new combination he requested to be returned to streptomycin.

Case 17: This 42-year-old Negro man was admitted February 24, 1955, with advanced disease of the right lung. For a year he received streptomycin with either isoniazid or para-aminosalicylic acid—or both some of the time. He made a rather remarkable improvement. However, with appearance of skin rash, dizziness, and hearing difficulty streptomycin was discontinued. Isoniazid and Terramycin were then presented. Symptoms disappeared rather quickly, but after a month he requested return to streptomycin.

Terramycin in Combination with Para-Aminosalicylic Acid

In more than an occasional case, difficulties develop which make the use of any of the major antituberculosis agents unfeasible. The use of para-aminosalicylic acid alone in such cases has been reported, but its effectiveness has not been remarkable. The combination principle is often lost sight of here although it is fully as important as in considerations of the major agents, especially when the need for withholding a major agent may possibly be only temporary. The following case reports of the use of Terramycin in combination with para-aminosalicylic acid, despite the limited number of patients thus far studied, are included because of unexpectedly favorable responses seen in most of them. When none of the major agents can be used, the possibilities of a combination of the lesser agents should not be ignored.

Case 18: This 54-year-old man was first seen in February, 1953 with advanced bilateral upper-lobe lesions, more marked with cavitation in the left lung. He was given streptomycin and para-aminosalicylic acid, but could not tolerate streptomycin after two and a half years. He was then put on Terramycin and para-aminosalicylic acid. For six months, the lesions remained stationary and the medication did approximately the same for him as other combinations before.

Case 19: This 44-year-old man was first here in August, 1954 with advanced pulmonary disease involving mostly the right upper and middle lobes. He was treated with streptomycin and para-aminosalicylic acid. After a year streptomycin was discontinued because it caused marked dizziness and urticaria. After changing to Terramycin and para-aminosalicylic acid he apparently did well during the three months he was observed before being transferred to another sanatorium. His sputum was still positive at that time. It was felt that the Terramycin plus para-aminosalicylic acid combination was at least equally as effective as his previous medication.

Case 20: This 39-year-old woman was admitted in February, 1954 with advanced right upper-lobe lesion, with cavitation and positive sputum. She was put on streptomycin, para-aminosalicylic acid and isoniazid. After 16 months sputum conversion had occurred, but the lesion in the right upper lobe showed unsatisfactory clearing. Right

phrenic nerve crush resulted in satisfactory rise of the right side of the diaphragm, and the same drug combination was continued for eight additional months. However, the disease was only slowly clearing. Two years after treatment had begun, drugs were changed to Terramycin and para-aminosalicylic acid, because streptomycin caused nausea and vomiting. After four months, she seems to be doing at least as well as on previous combinations.

Case 21: This 62-year-old Negro man was admitted in November, 1952 with positive sputum and far-advanced bilateral lesion involving both the left and right upper lobes. Streptomycin and isoniazid were used for nearly three years, but an eczematoid skin eruption then developed and these agents had to be discontinued, despite positive sputum and the fact that the right upper-lobe lesion particularly had cleared well. Terramycin and para-aminosalicylic acid were started, together with pneumoperitoneum and right phrenic nerve crush. During the five months this combination was used he made a much better improvement than on previous rest and streptomycin. Sputum remained positive, but clearing of the right upper lobe was most satisfactory. Recently he was returned to streptomycin and para-aminosalicylic acid. In this case, Terramycin offered help in a crucial time when other drugs could not be used.

Case 22: This 46-year-old Negro man was admitted in September, 1954 with extensive disease throughout the left and lesser infiltrations in the right lung. He was given streptomycin and isoniazid. After nine months, severe peripheral neuritis developed together with diffuse eczematoid lesions of the skin of both legs and arms. Streptomycin and isoniazid were discontinued and Terramycin and para-aminosalicylic acid started and given for almost three months. In addition, he was given pneumoperitoneum. When this treatment did not stop progression of the disease, he was again started on streptomycin, but it did no more than the Terramycin, possibly less, and he still could not tolerate it. During the subsequent six months pneumoperitoneum, viomycin and Terramycin have been employed but the condition continues to progress.

Case 23: This 54-year-old man gave a history of having had two coronary-thrombosis attacks. He was admitted in February, 1955 with extensive tuberculosis throughout the left lung with cavitation. He was first treated with streptomycin and para-aminosalicylic acid and was changed to Terramycin and para-aminosalicylic acid after six months. In addition, pneumoperitoneum has been utilized. He has been hemorrhaging and streaking through all this time. His general condition is slightly improved; his lung condition is basically unchanged. Terramycin has done neither more nor less than streptomycin before it.

Case 24: This 50-year-old man was admitted in June, 1954. He had previously been in an institution for a neuropsychiatric condition. He had bilateral nodular infiltration of the upper lobes in a moderately active state. He received streptomycin, para-aminosalicylic acid, and isoniazid but streptomycin was discontinued after about eight months, when he complained of dizziness—which it may or may not have caused. He was continued on isoniazid and para-aminosalicylic acid for six months longer. Because hepatitis developed, medication was stopped. After three months without medication, Terramycin and para-aminosalicylic acid were begun, and he is doing well. He is improving and approaching the arrested state. He is doing at least as well on this combination as on previous combinations and seems to have no untoward effects from it.

Other Observations

In a few cases difficulties mount to prevent the use of any of the regular antituberculosis drugs, and in some of these it may be possible that Terramycin is tolerated. It would be overoptimistic to anticipate significant benefit from the use of Terramycin alone, but the following experience of such a case suggests that the possibility of achieving a favorable result from such therapy should not be passed over without trial.

Case 25: This 60-year-old man was admitted in January, 1947 with far-advanced silicotuberculosis involving both upper lobes, with extensive honeycombing and cavitation in the right upper lobe. He was treated with streptomycin in combination with para-aminosalicylic acid or isoniazid, and for some periods with all three of these drugs, in repeated courses over the following eight years. Streptomycin then began to affect his eyes, para-aminosalicylic acid could no longer be tolerated, and isoniazid seemed to upset his gastrointestinal tract. He was, therefore, started on Terramycin and has now been receiving it alone for over a year. Twice attempts have been made to add another and more active agent, but neither streptomycin nor isoniazid could be tolerated. Little if any roentgenographic change has been observed during the year he has been on Terramycin alone, but clinically he is distinctly improved—and this is

the more remarkable since, at least during the previous year, three basic agents did little or nothing for him.

There remains to be mentioned briefly the usefulness of Terramycin, not primarily for its antituberculosis activity, but for its effectiveness against non-tuberculous infections in patients with tuberculosis. It holds a unique position among the antibiotics—its broad-spectrum activity against a wide variety of pathogens is unsurpassed among the commonly used antibiotics, and at the same time its activity against the tubercle bacillus which is shown by none of the other more general antibiotics. It is for this reason that the use of Terramycin is especially advantageous when any of the common non-tuberculous infections occur in a patient with tuberculosis—for the benefit of its action against the tubercle bacillus is added to its effectiveness against the pathogens that are its primary target. Cases in which advantage may be taken of this dual role of Terramycin are not uncommon, and it is this usefulness that is the issue in this final case report.

Case 26: This 67-year-old Negro man was admitted in July, 1953 with a left-sided lesion—and what later was found to be extensive mediastinal empyema. Streptomycin was poorly tolerated, and because of a high fever it was considered advisable to use Terramycin as the combined agent. Results by the end of two months were most gratifying. However, he refused further medication and any kind of surgical treatment. When the treatment was stopped his condition rapidly deteriorated, and he died within a month. It is believed that in this case of severe complicating infection Terramycin was at least equal, if not superior, to other agents, and it is thought that surgical drainage and antibiotics probably could have saved his life.

In addition to the foregoing 26 cases, in which Terramycin was used for periods of one month or longer (several for a year or more), 16 other patients received Terramycin for varying shorter periods—1 to 20 days. The short duration in these cases precludes any attempt at evaluating its effect on the tuberculous infection. In seven of the 16 short-term patients Terramycin was discontinued because of nausea, gastric distress, or diarrhea. Diarrhea developed in three of these. In four other patients treatment was terminated within less than a month either because of death or discharge from the sanatorium; and Terramycin was not continued in any of these after discharge so far as is known. The remaining five of this group of 16 received Terramycin for strictly temporary conditions, and it was not proposed that this agent be used longer than required in the particular circumstances. In one case dizziness had developed from streptomycin, but this reaction disappeared within a week after substituting Terramycin for the streptomycin and the patient was returned to the previous treatment. In the four other cases a temporary high fever had developed, and as the origin of the fever was not evident the possibility that it might represent either breakdown of tuberculous lesions or secondary infection made the use of Terramycin an expedient precaution because of its probable beneficial effect whichever the actual cause of the fever. In these cases Terramycin was added to the continued use of streptomycin and other antituberculosis drugs, and in all of these cases defervescence occurred promptly after addition of Terramycin—and this consistent response strongly suggests that the use of Terramycin is indeed warranted in these circumstances.

SUMMARY AND CONCLUSIONS

The treatment of tuberculosis is still a complex and prolonged procedure, and no single drug has been found to be effective over a protracted period.

Present treatment usually includes a primary agent which exerts the major tuberculostatic action, the main choice still being between streptomycin and isoniazid. To this primary agent we usually add an ancillary drug, which aids in preventing emergence of organisms resistant to the primary drug. Para-aminosalicylic acid has been the drug of choice for this purpose, but its usefulness is restricted by the frequent occurrence of gastro-intestinal irritation in proper dosage.

Other antituberculosis agents have been used to lesser extent, such as viomycin and, more recently, cycloserine, but we still are sorely in need of an alternative ancillary agent for the many cases in which para-aminosalicylic acid cannot be tolerated or is no longer effective.

We have used Terramycin as an adjunct to isoniazid in 16 patients, and it was our impression that this combination was fully as effective as, and in a few instances, perhaps more so than any other combination of antituberculosis drugs. The use of Terramycin as an ancillary drug together with isoniazid, streptomycin, or viomycin is encouraged for all patients in whom para-aminosalicylic acid cannot be employed.

RESUMEN

El tratamiento de la tuberculosis es aún un procedimiento complejo y prolongado y no hay droga sola que sea efectiva por perfodos largos.

El tratamiento al presente generalmente incluye un agente primario que ejerce la mayor acción tuberculostática siendo la elección principal entre estreptomicina e isoniacida. A esta droga principal nosotros habitualmente agregamos una droga auxiliar que ayuda a prevenir la aparición de organismos resistentes a la droga principal.

Para este abjeto el PAS es la droga de elección, pero su utilidad está restringida por la irritación gastrintestinal que produce a dos adecuada.

En mayor extensión otras drogas antituberculosas se han usado, tales como la viomicina, más recientemente la cicloserina, pero aún estamos necesitando mucho de un agente alternativo que pueda usarse en vez del PAS no tolerado o ya ineficaz.

Hemos usado la terramicina como adyuvante de la isoniacida en 16 enfermos y nuestra impresión ha sido que la combinación es taneficaz y en algunos casos más eficaz que otras combinaciones.

El uso de terramicina como droga auxiliar, junta con la isoniacida, estreptomicina o viomicina, es de alentarse en todos los enfermos en quienes ya no se puede usar PAS.

RESUME

Le traitement de la tuberculose reste encore complexe et demande à être suffisament prolongé. Aucune drogue seule ne s'est montrée efficace pendant une période d'essai.

Le traitement actuel comprend généralement un agent primaire qui exerce l'action tuberculostatique essentielle, le choix se faisant principale-

ment entre la streptomycine et l'isoniazide. A cet agent essentiel, nous ajoutons habituellement un produit mineur, qui empêche les microbes de devenir résistants á la première médication. L'acide P.A.S. a été le produit de choix utilisé dans ce but, mais son usage est limité par l'apparition fréquente de troubles gastro-intestinaux lorsqu'on utilise les doses convenables.

D'autres agents antituberculeux ont été employés sur une moins grande échelle, tels que viomycine, et plus récemment cyclosérine, mais nous avons encore un pressent besoin d'un agent mineur auxiliaire pour les nombreux cas dans lesquels le P.A.S. ne peut pas être supporté on n'est plus efficace.

Nous avons utilisé la Terramycine avec l'isoniazide chez 16 malades, et nous avons eu l'impression que cette association s'est montrée tout á fait efficace dans la même proportion et dans quelques cas peut-être davantage, que toute autre association de médications antituberculeuses. L'emploi de la Terramycine comme agents auxiliaire associé à l'isoniazide, à la streptomycine, ou á la viomycine, est conseillée pour tous les malades chez qui le P.A.S. ne peut pas être utilisé.

ZUSAMMENFASSUNG

Die Behandlung der Tuberkulose stellt immer noch ein komplexes und langdauerndes Vorgehen dar, und über einen sehr langen Ze.traum hat sich noch kein einzelnes Arzneimittel als wirksam erwiesen. Die gegenwärtige Behandlung umfasst gewöhnlich einen Grundstoff, der die grössere tuberkulostatische Wirkung ausübt, und die erste Wahl liegt immer noch Streptomycin und INH. Zu dieser Grundlage fügen wir für gewöhnlich ein ergänzendes Mittel, das dazu beiträgt, das Auftreten von gegen das erste Mittel resistenten Keimen zu verhindern. PAS war zu diesem Zweck das Mittel der Wahl, aber ihr Nutzen ist eingeschränkt durch das häufige Auftreten von Magen-Darmstörungen bei ordnungsgemässer Dosierung.

Andere antituberkulöse Stoffe sind in geringerem Umfang zur Anwendung gelangt, so wie z.B. Viomycin und kürzlich erst Cycloserin, aber wir bedürfen dringend eines alternativ ergänzenden Stoffes für die vielen Fälle, in denen PAS nicht vertragen werden kann oder nicht mehr wirksam ist.

Wir haben Terramycin zusätzlich zu INH bei sechzehn Kranken angewandt und hatten den Eindruck, dass diese Kombination von mindestens ebensolcher und in einigen wenigen Fällen vielleicht sogar noch besserer Wirksamkeit war als irgend eine andere Kombination von antituberkulösen Mitteln. Der Einsatz von Terramycin als Ergänzungsmittel zusammen mit INH, Streptomicin oder Viomycin gibt allen den Patienten einen Auftrieb, bei denen PAS nicht zur Anwendung kommen kann.

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Partial Air Replacement During Thoracentesis: Its Value in Diagnosis and Treatment

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Replacement of fluid removed from the pleural cavity, partially by air, is a most valuable procedure. Its use has been known for a great many years, but for various reasons, it has been used infrequently in this country. The advantages in diagnostic roentgen ray work are great, and its usefulness in making possible the removal of large quantities of fluid at one time, is important. If such considerations are true, why then has it not been universally used?

The chief reason if not the sole one, has been due to the misinterpretation of the report of the Empyema Commission following the great Influenza epidemic in 1918. At that time there were a great many cases of empyema. Most of them were due to the Streptococcus hemolyticus, and accordingly when the empyema developed it did so while the pneumonic process was still active. Also in this type of infection the inflammatory process remains generalized for a long time, and is really a suppurative pleurisy, for empyema literally means a localized collection of pus. Many of these patients, treated by open drainage, died. The induction of open pneumothorax in the presence of underlying pneumonia, and mobile mediastinum, inevitably is followed by death. However, in the pneumococcus empyemas, with walled off pus and a fixed mediastinum, and the pneumonic process resolved, open drainage does no harm but leads to recovery. The Empyema Commission pointed out the fallacy of using open drainage in cases of streptococcus empyema, and explained the reasons for it. Unfortunately, many doctors in this country interpreted this report as a condemnation of open drainage in general. Furthermore, they came to believe that the mere presence of air in the pleural cavity was bad, in spite of their knowledge of the pneumothorax treatment of tuberculosis. How they could come to such a conclusion is hard to understand, but having taught in three medical schools, and having had contact with graduates from many others, I know that what I have said is true.

So much for the apparent reasons why this simple, and innocuous procedure has not been used. What can be accomplished by its use? Its greatest value lies in the aid given in roentgen ray visualization of shadows obscured by fluid in the pleural cavity. When one aspirates this fluid, unless most of it is removed, the only change noted in the roentgen ray is in the position of the mediastinum. Any nodule on the surface of the lung or on the parietal pleura, will not be visualized. However, if the fluid is even partially replaced with air it will fall away from the surface of the lung to the bottom of the pleural cavity. Then, if the patient is put in various positions, with the air uppermost, the surfaces of the lung and the

parietal pleura will be plainly visualized. The accompanying reproductions of roentgen rays from a case of hemothorax of unknown etiology will illustrate what I have just said. The procedure demonstrated the presence of peripheral nodules after all other studies, including bronchoscopy, had failed to show anything except the bloody pleural fluid. The diagnosis of metastatic carcinoma of the lung and pleura was thus established. Figures 1, 2, and 3.

FIGURE 1

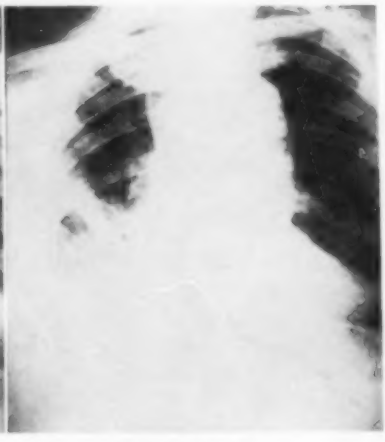

FIGURE 2

Figure 1: Roentgen ray of chest showing massive right pleural effusion.—*Figure 2:* Roentgen ray of chest showing residual fluid in lower part of right pleural cavity and return of mediastinal shadow to midline.

FIGURE 3: Roentgen ray examination of chest to show details in right lower chest. Note rounded shadows on lower parietal pleura and over diaphragm, and showing through lowermost part of the lung.

The first time I saw air replacement of pleural fluid for diagnostic purposes was in 1921, as an intern at the Presbyterian Hospital in New York. We had all been admonished never to allow any air to enter the pleural cavity during thoracentesis. Then, Dr. Hans Jacobaeus of Stockholm visited the hospital to demonstrate his use of the thoracoscope. He examined a patient with bloody pleural effusion on whom no diagnosis had been made. In the chief operating amphitheatre the patient was placed on an operating table. Dr. Jacobaeus injected a small amount of novocain and then inserted a rather large trocar and cannula. When the trocar was removed bloody fluid escaped under pressure. He rolled the patient on his back in order for the fluid to flow out more easily and then turned him back on his side so that air could flow into the pleural cavity. He repeated this maneuver until practically all the fluid had been removed and been replaced with air. The thoracoscope was then inserted and he could see carcinomatous nodules scattered over the surface of the lung and the parietal pleura. A diagnosis of carcinoma of the lung and pleura was thus made. In spite of this dramatic demonstration no one was apparently influenced to follow Dr. Jacobaeus' lead, and it was not until 1929, when in Dr. Graham's chest clinic in St. Louis that I saw Dr. Singer use air replacement of pleural fluid. He told me then that the technique had long been in use in Germany. Since that day I have used this procedure and have exhorted my students, interns, and associates to do the same, but without success.

Although the chief value of air replacement has to do with roentgen ray visualization, the procedure has real merit also in other respects. When one aspirates fluid from the pleural cavity the negative pressure in it is increased. If the patient is in the usual sitting position, and a large amount of fluid is withdrawn, he will usually faint as the result of the shift of the mediastinum, and the effect on the circulation. On the other hand, if air is allowed to flow back into the pleural cavity as the fluid is withdrawn, the change in pressure will be so slight that no symptom will develop. It is not necessary to measure the amount of air that is allowed to flow into the pleural cavity. All one need do is to disconnect the syringe from the needle from time to time and allow air to be sucked into the pleural cavity. Unless one is using a large cannula and leaves it open for a long time no harm can result. Using this technique one can completely evacuate the pleural cavity without disturbing the patient in any way. While it is the custom to have the patient sitting upright when thoracentesis is being done, apparently in order to remove all of the fluid, this is a bad practice. It is practically never necessary to remove all of the fluid from the chest, and about as much can be removed by having the patient lying on the side and rolling over backward, as by having him sit up straight. It is far more comfortable for the patient to lie on his side if he is sick and weak. The complete evacuation of the pleural fluid at one sitting makes it possible to do the aspirations at less frequent intervals.

Another advantage of partly replacing the fluid with air is that the negative pressure does not build up and therefore it is easier to withdraw the

fluid. Even the aspiration of blood and pus is aided, but in these cases it is important to remove the air at the end of the aspiration so that no pocket of pneumothorax remains which might lead to a localized pocket of empyema, or prevent full re-expansion of the lung.

SUMMARY

Partial replacement of fluid withdrawn on thoracentesis allows one to withdraw large amounts of fluid at one time without upsetting the patient, because changes in intrapleural pressure are so little. It also causes fluid covering the lung to fall from it, and thus allows the x-ray visualization of the surface of the lung and of the parietal pleura. This procedure should be used in all cases of pleural effusion, but where there is an empyema or hemothorax, it is important not to allow any air to remain in the pleural cavity. The air is allowed to enter the pleural cavity freely through the needle in the chest wall when the syringe is disconnected from it. If a needle of size 15 or smaller is used it is not necessary to measure the amount of air.

RESUMEN

La substitución por aire del líquido extraído por toracentesis, permite extraer grandes volúmenes de líquido de una vez sin molestar al enfermo porque los cambios en la presión intrapleural son pequeños.

También permite que el líquido que cubre el pulmón caiga y así permite observar la superficie del pulmón y de la pleura parietal por los rayos X. Este procedimiento debe usarse en todos los casos de derrame pleural, pero cuando hay empiema o hemotórax es importante que no se deje aire en la cavidad pleural.

El aire se deja libremente en la cavidad pleural entrando con sólo que se desconecte la aguja de la jeringa. Si la aguja es de calibre 15 o menos, no es necesario medir el volumen de aire.

RESUME

Le remplacement partiel du liquide ponctionné en cas de thoracenthèse par de l'air permet de retirer d'importantes quantités de liquide en une seule fois sans dommage pour le malade, car ainsi les modifications de la pression intra-pleurale restent assez faibles. Cela permet aussi de débarrasser le poumon du liquide qui le recouvre et assure la visibilité radiologique de la surface pulmonaire et de la plèvre pariétale. Ce procédé doit être utilisé dans tous les cas d'épanchement pleural, mais en cas d'empyéme ou d'hémothorax, il es important de ne pas laisser la moindre quantité d'air dans la cavité pleurale. L'air peut entrer librement dans la cavité pleurale par l'aiguille dans la paroi thoracique, au moment où elle n'est plus emmanchée dans la seringue. Si une aiguille de taille 15 ou plus petite est utilisée, il n'est pas nécessaire de mesurer la quantité d'air.

ZUSAMMENFASSUNG

Partielle Verlagerung der bei der Thoraxpunktion abgesaugten Flüssigkeit macht es möglich, grosse Flüssigkeitsmengen auf einmal abzusaugen, ohne den Patienten aufzusetzen, weil die Veränderungen des intrapleu-

ralen Druckes so gering sind. Sie veranlasst auch die die Lunge überdeckende Flüssigkeit, sich zu senken, und ermöglicht so die röntgenologische Darstellung der Lungenoberfläche und der parietalen Pleura. Dieses Vorgehen sollte bei allen Fällenvon pleuralem Erguss angewandt werden; liegt jedoch ein Empyem oder ein Haemothorax vor, so ist es wichtig, nicht zuzulassen, dass irgendwelche Luft in der Pleurahöhle zurückbleibt. Die Luft hat die Möglichkeit, in die Pleurahöhle frei durch die Nadel in der Brustwand zu gelangen, wenn die Spritze von ihr entfernt ist, Wird eine Nadel der Grösse 15 oder weniger benutzt, ist es nicht nötig, die Lufmenge zu messen.

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The Effect of Acetazolamide* on Arterial Carbon Dioxide Tension in Respiratory Acidosis: A Preliminary Report

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Carbon dioxide retention in hypoventilation resulting from bronchitis or bronchopneumonitis leads to respiratory acidosis. Non-compensated acidosis modifies the blood pH, thereby altering the acid base balance. It is not unusual to find respiratory acidosis in patients with chronic respiratory insufficiency. Cournand[1] reported the successful treatment of emphysematous patients with hypercapnia using either artificial respiration or a carbonic anhydrase inhibitor such as acetazolamide. Several investigators, including Nadel[2] and Taymor et al[3] found that acetazolamide lowers the carbon dioxide tension in the arterial blood. They reached this conclusion by determining the pH and total carbon dioxide content of the arterial blood, using the Henderson-Hasselbalch equation. This study was undertaken to evaluate the significant results of this therapy in Chile. Therefore, we have determined the carbon dioxide tension in the arterial blood both before and after administration of acetazolamide to patients with respiratory acidosis.

Method

Following a half hour rest period in a supine position, the oxygen and carbon dioxide tension of blood drawn from the radial artery, were determined in four patients with chronic pulmonary disease (silicotuberculosis, bronchial asthma, bronchiectasis, emphysema, pulmonary heart disease) : complicated by acute bronchitis or bronchopneumonitis. The blood was extracted with a Luer-lok syringe, with heparin in the dead space. It was then equilibrated with a bubble of alveolar air, (the composition of which was controlled in a Haldane chamber) in a Roughton-Scholander apparatus,[4] at a temperature of 37.5°C. in these studies we followed the technique of Riley et al.[5] Plasma electrolytes were also controlled by direct technique in a Lange flame photometer. Benedict and Tissot spirometers were used to measure pulmonary volume and ventilatory capacity, respectively. Values corrected to BTPS are expressed as percentages of the predetermined levels.[6] Diuresis and weight of patients were controlled. A Singer and Hastings nomogram was used to measure the pH of arterial blood, with values of carbon dioxide arterial tension, hematocrit, and Fenn's diagram for calculation of arterial carbon dioxide content, when this was not determined in a Van Slyke apparatus.

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*Kindly supplied as Diamox by Lederle Laboratories, Pearl River, New York.
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TABLE I

BLOOD STUDIES AND MAXIMUM BREATHING CAPACITY OF FOUR PATIENTS WHO RECEIVED ACETAZOLAMIDE

Patient No.	Date	Sex	Age	CO_2 Arterial Pressure mm. Hg.	O_2 Arterial Pressure mm. Hg.	Arterial Content CO_2 Vol. per cent	Arterial Blood pH	Hematocrit	H +	Sat. per cent *	MBC (a)
1	6.14.56	F	60	67						60	39
	6.21.56			46	78	52	7.36	42	437	94	
	6.30.56			46	70	52				93	
	7.12.56			41	74	48	7.40		400	94	57
2	6.19.56	F	61	52	51	55	7.32	46	478	80	31
	6.26.56			44	56	51	7.34		457	85	
	7. 3.56			‡50	55	54	7.30		520	80	
	7.12.56			38	79	47	7.40		400	95	50
3	6.11.56	M	65	67	57	60	7.24		575	80	− + °
	6.18.56			45	72	51	7.36		437	93	+ °
4	8. 1.56	M	58	63	33	60	7.26	50	550	70	20
	8. 3.56			58	47	58	7.29		513	80	°
	8. 6.56			37	71	47	7.42		387	94	74

H + concentration of hydrogen ions 10-8 molecules per liter

* saturation percentage of arterial oxihemoglobin

MBC maximum breathing capacity: percentages of predetermined value expressed in ml. (BTPS)

(a) see Table III

‡ treatment discontinued. Normal CO_2 arterial pressure resulted from a second course of therapy

° clinical estimate of pulmonary ventilation.

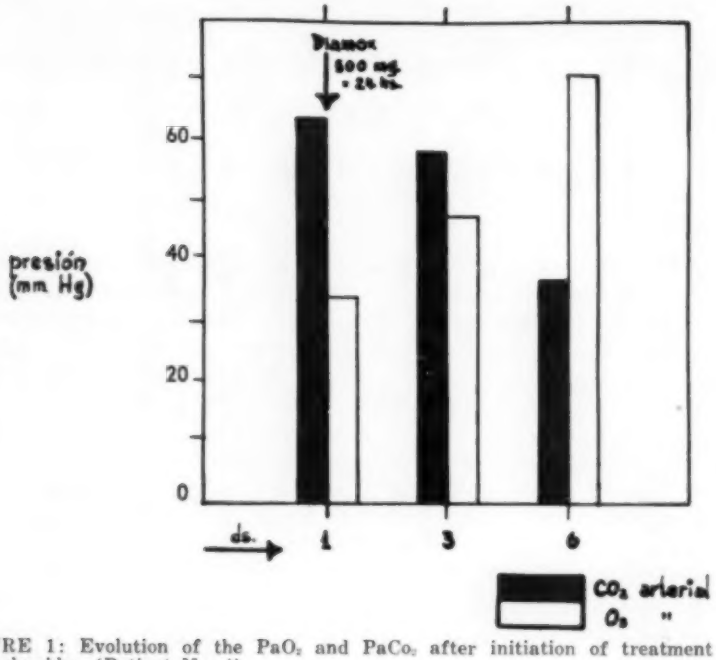

FIGURE 1: Evolution of the PaO_2 and $PaCo_2$ after initiation of treatment with acetazolamide. (Patient No. 4).

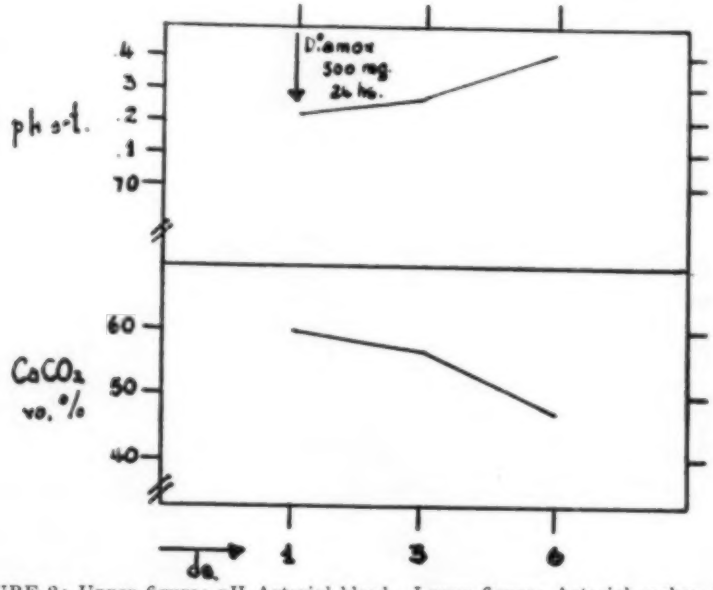

FIGURE 2: Upper figure: pH Arterial blood. Lower figure: Arterial carbon dioxide content. (Patient No. 4). See text.

TABLE II

CORRELATION BETWEEN ELECTROLITOGRAM, WEIGHT AND SYMPTOMATOLOGY OF PATIENT NO. 1 BEFORE AND AFTER INITIATING ACETAZOLAMIDE THERAPY.

Patient No.	Date	K	Na	Cl	Alkaline Reserve	Weight Kilos	Cyanosis	Stertor	Dyspnea	Mental Symptoms
1	6.14.56	3.3	145	102	28.0	78	++	++	++	Confusional state
	6.21.56	4.87	125	95	20.27	71	++	+	—+	Normal
	6.30.56	3.02	137	95	23.8	72	—	—+	—	Normal
	7.12.56	*2.06	125	99	15.38	74	—	—+	—	Normal

The electrolitographic values are expressed in mEq./L.

*alterations in repolarization of electrocardiogram

TABLE III

MODIFICATIONS IN VENTILATION AFTER ADMINISTRATION OF ACETAZOLAMIDE

Date	Vital Capacity Per cent of Predetermined Value	Ventilation (L/min/m²)	Ventilation (L/min/m²) Exercise	Frequency		VT	Maximum Breathing Capacity
				Rest	Exercise		
Patient No. 1							
				Control			
6.14.56	22	4.3	7.2	32		240	39
				Diamox			
6.30.56	46	5.9	11.1	24	46	425	58
7.12.56	47	6.6	16.6	23	37	494	79
Patient No. 2							
				Control			
6.19.56	66	5.3	10.3	19	26	500	31
				Diamox			
6.25.56	79	7.3	8.6	19	28	700	45
7.12.56	63	8.9	12.6	19	22	736	50

Acetazolamide was administered in doses of 500 mg. daily for three days, with therapy suspended on the fourth day. This regimen was continued until the carbon dioxide arterial tension was restored to normal average levels. Total dosage of acetazolamide ranged from three to seven grams. Hemograms were done to detect possible bone marrow depression as reported by Underwood.[7] Prior to acetazolamide therapy, subjects had been treated with antibiotics, mucolytics and bronchodilators over a period of not less than eight days, with no significant clinical response.

Results

Table I shows the fluctuations in the different values, both before and during acetazolamide administration. The significant decline in carbon dioxide arterial tension toward average normal values is apparent, as well as that in the saturation values of the oxihemoglobin arterial blood pH. The change in maximum breathing capacity and the reduction of total carbon dioxide concentration are also worthy of mention.

Table II sets forth controls for patient No. 1, in whom were noted the decrease in alkaline reserve as well as the tendency to reduction of the potassium and sodium ions. This, together with the decrease of cyanosis, headache and confusion, may be correlated with the values shown in Table I. The decrease in potassium in this case was so great that it led to modifications in the electrocardiogram, with changes in repolarization which reversed when treatment was discontinued.

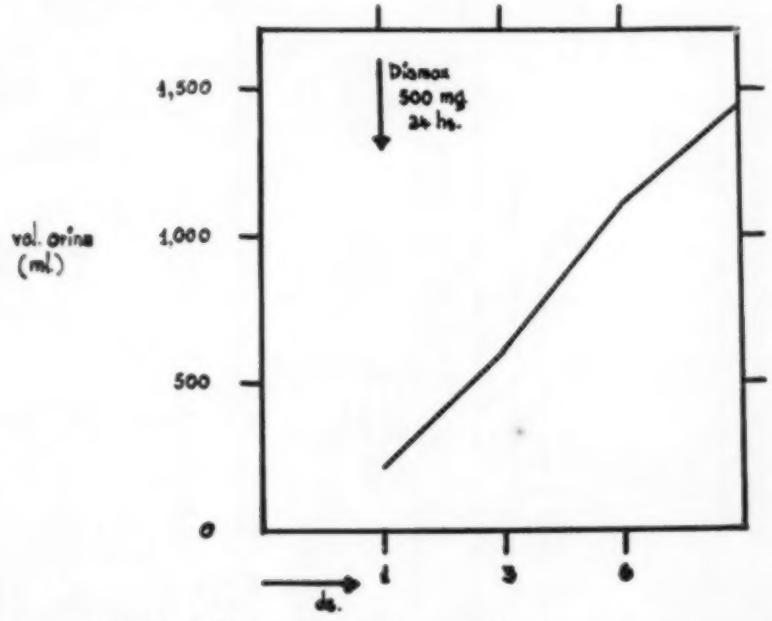

FIGURE 3: Diuretic effect of Acetazolamide (Patient No. 4).

Figure 1 shows the evolution of carbon dioxide and oxygen arterial tension in patient No. 4, after initiation of treatment with acetazolamide. Figure 2 gives the variations registered in the arterial blood pH, which showed an increase, and of the arterial carbon dioxide content, which decreased. In this patient there was an obvious diuretic effect, as may be noted in Figure 3. Maximum breathing capacity values appear in Figure 5, shown as percentages of the predetermined values, both before and after acetazolamide. (See Table III).

Discussion

In the presence of increased carbon dioxide tension, the body calls on the different mechanisms which tend to increase the bicarbonate, thus avoiding an abrupt acidification of the pH. Of these compensating mech-

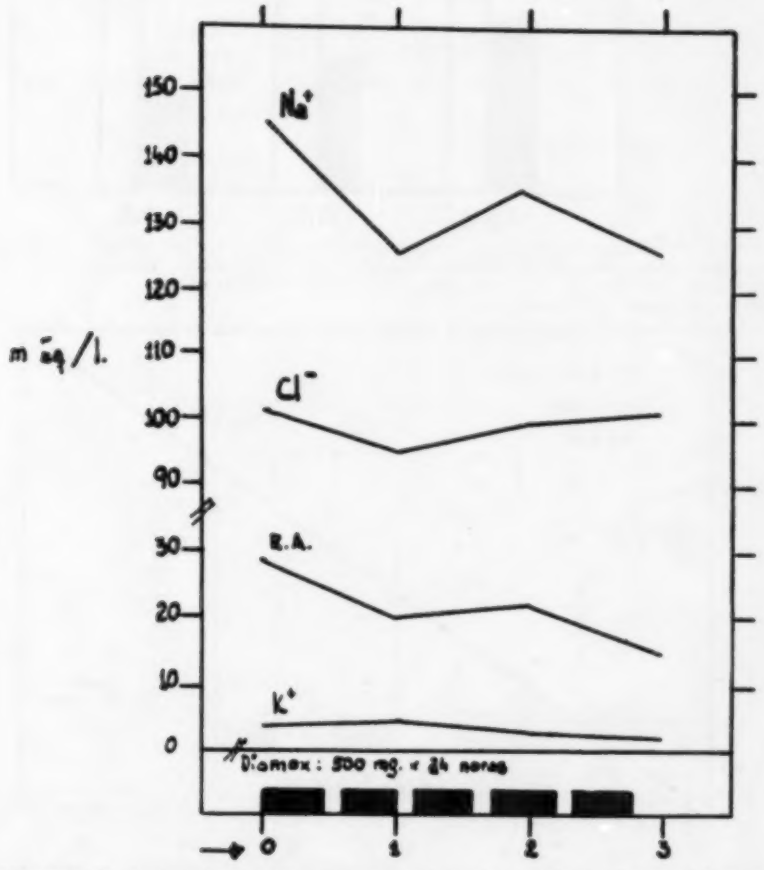

FIGURE 4: Evolution of electrolitogram in Patient No. 1 after initiation of treatment with acetazolamide.

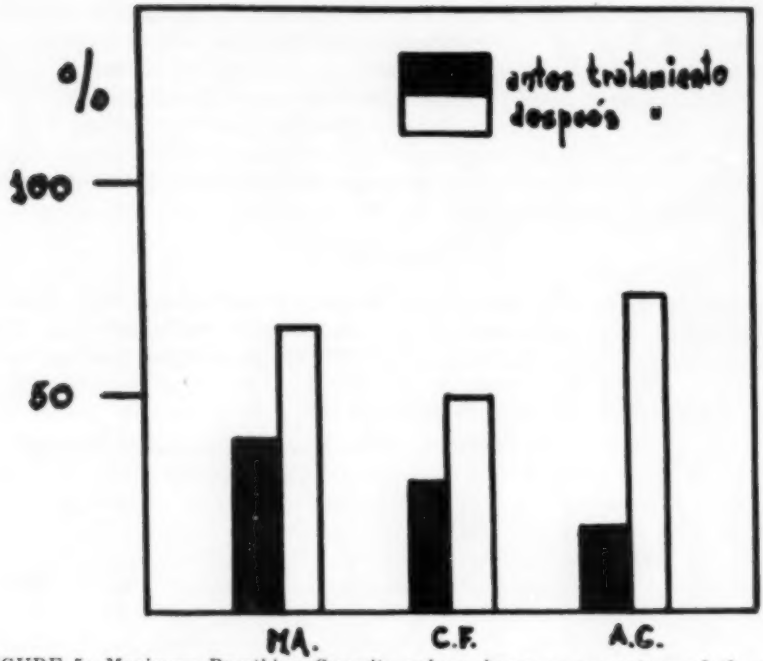

FIGURE 5: Maximum Breathing Capacity values shown as percentage of the predetermine values (Ml., B.T.P.S.) before and after acetazolamide treatment.
M.A.—Patient No. 1; E.F.—Patient No. 2; A.C.—Patient No. 4
In black; before treatment values.

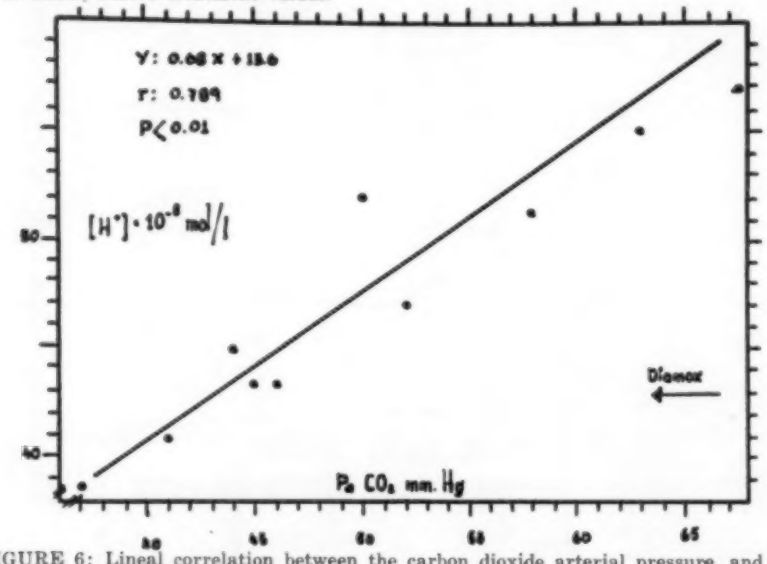

FIGURE 6: Lineal correlation between the carbon dioxide arterial pressure, and the concentration of hydrogen ions in arterial blood in patients with respiratory acidosis and its evolution in time with acetazolamide treatment. The whole line represents the equation.

anisms, we would first mention the purely physiochemical which affect the blood and tissues, with participation of the various buffer systems, especially those which also act on the hemoglobin and protein. To these mechanisms are added the diffusion of cellular bicarbonates, plus the transfer of the chloride and phosphate ions, lactates and exchange of sodium and potassium ions.[8] Taymor et al[3] have shown that renal reabsorption of the bicarbonate radical (HCO_3) is in direct proportion to the carbon dioxide arterial pressure.

Thus, it appears that the initial action on the respiratory center is governed by Gray's equation.[9] However, this stimulating action does not prevail in pronounced hypercapnia, particularly if increased carbon dioxide arterial pressure is added to the inhibiting effect of the increased bicarbonate levels on the respiratory center.[10, 11] We have found there is a lineal correlation (r:0. 789) between the carbon dioxide arterial pressure, and the concentration of hydrogen ions in arterial blood, an equation similar to that described by Gray.[9] (See Figure 6).[12]

$$H+ = 0.68\ CO_2 \text{ arterial pressure} + 13.6$$

These findings, together with the hypoventilation manifested by pa-

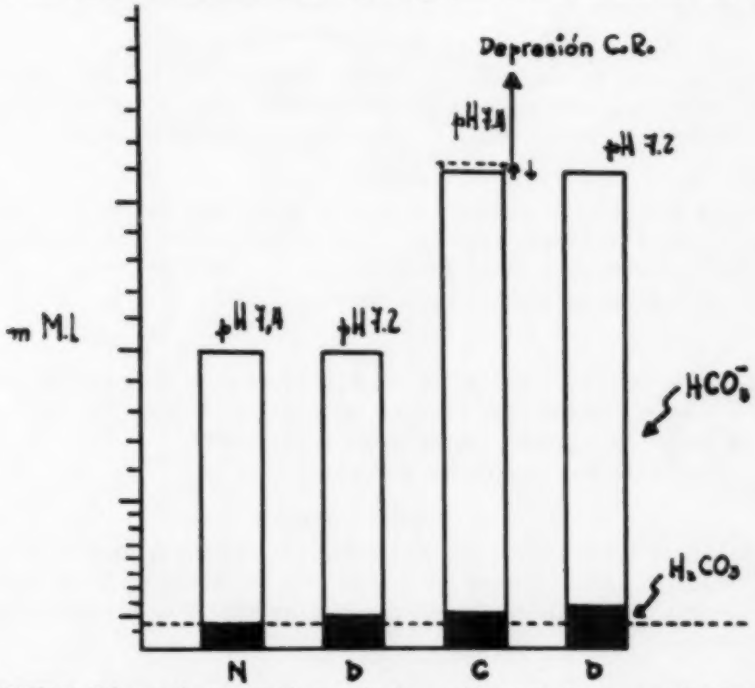

FIGURE 7: Scheme of compensating mechanisms which tend to increase the bicarbonates in respiratory acidosis with depression action on the respiratory center:

N — normal values
D — acidosis values
C — compensating values
See text for explanation.

tients with hypercapnia, lead us to believe that the modifications of the buffer properties in the blood and tissues produce a depressing action on the respiratory center. If we add the intra-extracellular ionic modifications which lead to alterations of the membrane potential, we might explain the lack of response of the respiratory center to stimuli to which it ordinarily reacts. The hypoxia factor will act in much the same manner, as it leads to a modification of the ventilatory response.[13] In continued carbon dioxide retention, at the expense of the hypoventilation produced by physiochemical changes in the respiratory center, and the effects it may sustain from the fluctuations of the bicarbonates as well as the obstructive mechanisms of the bronchioli, we find that arterial blood pH will reach a new level in accordance with the Henderson-Hasselbalch equation. In Figure 7 we have attempted to show these various changes. At this point acetazolamide acts on the bicarbonates, first in the blood and tissue buffer systems (direct action on the respiratory/center?), progressively reestablishing the sensitivity of the respiratory center, thus permitting pulmonary elimination of the carbon dioxide. This, together with the renal mechanisms affected by this carbonic anhydrase inhibitor, eliminates the bicarbonate ions.

SUMMARY

The decrease in carbon dioxide arterial tension after initiation of treatment with acetazolamide in respiratory acidosis occurring in the decompesation stage of chronic respiratory insufficiency, is demonstrated.

RESUMEN

1. Se demuestra el descenso de la PaCO2 después de iniciar el tratamiento con Diamox en la acidosis respiratoria producida en la etapa de descompensación de la insuficiencia respiratoria crónica.

2. Se discuten los mecanismos de acción.

RESUME

1. On demontre la descente de la PaCo2 aprés avoir commencé le traitement avec le Diamox dans l'acidose respirátoire produite pendent la decompensation de l'insufissance respiratorie chronique.

2. On discute les mechanismes d'action.

ZUSAMMENFASSUNG

Nachweis der Abnahme der arteriellen CO_2-Spannung nach Einleitung der Behandlung mit Diamox bei respiratorischer Acidose, wie sie auftritt im Stadium der Dekompensation einer chronischen, respiratorischen Insuffizienz.

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Is Streptomycin an Ineffective Antituberculous Therapy in the Absence of Acquired Host Resistance?

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To evaluate a new therapy is difficult. Its virtues frequently appear early, whereas its limitations are discovered later. It is just as important, however, to understand the limitations as it is the virtues of a therapeutic agent.

The purpose of this paper is to focus attention upon a limitation of streptomycin, namely, that streptomycin is an ineffective antituberculous agent in the absence of acquired host resistance. Since streptomycin was shown to be both tuberculostatic and bacteriocidal *in vitro*, and *in vivo*[1-4] except in the pathological tissues of chronic tuberculosis,[5, 6] it was to be hoped that streptomycin could be used as a prophylactic agent to prevent the development and the progression of tuberculosis in individuals who had been exposed to the disease.

The clinical symptoms of malaria can be prevented by the prophylactic use of quinine, quinacrine or chloroquine. There is good evidence that syphilis and gonorrhea can be prevented by the use of penicillin prior to exposure. Yet it appears that streptomycin, a tuberculostatic agent, when given simultaneous with or even prior to an injection of tubercle bacilli, fails to sterilize the tissues, and fails to prevent both the development of and the progression of tuberculosis.

History

Prior to chemotherapy and antibiotic agents, it was not uncommon for many tuberculous patients to make good recoveries on a regimen of bed-rest, a good diet and occasionally some aid from collapse therapy. Other tuberculous individuals have recovered without even the help of bed-rest, diet and collapse therapy. Many of these individuals have been wholly unaware that they were tuberculous, and have made recoveries without deviating from their normal daily activities. The above recoveries from tuberculosis without the aid of chemotherapy or antibiotic agents have been largely due to good natural and/or good acquired host resistance. These recoveries are verified by roentgenologists almost daily on discovery of cases of arrested tuberculosis without history of illness. It is also interesting to note here that some states show as many as twenty-five per cent of the deaths from tuberculosis have occurred in individuals who were apparently free or relatively free from symptoms, being unknown to the public health authorities prior to the receipt of the death certificates.[7]

Since the early reports of Hinshaw,[1-3] it has been generally accepted that streptomycin could exert a powerful effect upon the course of a tuberculous infection. The prompt recovery of early tuberculosis, the improve-

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ment, and the prolongation of life in chronic tuberculosis, and the life-saving effects in the fatal forms of tuberculosis, brought great enthusiasm for streptomycin, possibly more than it deserved. Some of the factors that had contributed to the rapidity of the recoveries and the improvements had been overlooked: Bed-rest, supportive diets and physiotherapy, natural and acquired host resistance, freedom from responsibilities and worries, combined therapies, and collapse and excisional therapies.

When streptomycin proved to be highly tuberculostatic *in vitro*, and when it was found that therapeutic blood levels were easily attained, it was natural to credit the agent for any clinical improvement achieved, and to forget that natural and acquired resistance and other factors might have played an important part.

While it has been just a decade since streptomycin was shown to be tuberculostatic, many limitations have been recognized:

Streptomycin usually proved toxic in more than one gram daily doses.

Streptomycin failed to clear the majority of cases of tuberculosis.

Streptomycin-treated tuberculosis has frequently relapsed within a few months.

Continued use of streptomycin has caused the micro-organisms to become resistant to it in a high percentage of cases.

Streptomycin can rarely be counted upon to cure tuberculosis without combining it with other forms of therapy.

The above list of limitations is not complete and will not be discussed further as it has been adequately covered in other writings. This paper will point out another limitation of streptomycin, discuss it briefly, and suggest methods of minimizing it.

Natural and Acquired Host Resistance

An animal which becomes infected with a disease such as tuberculosis, makes a great effort to overcome that disease by localization of the micro-organisms, phagocytosis, antibody response, encapsulation of the infected areas of tissue by fibrosis, etc. The animal's inherent ability to combat disease is its native or natural resistance. The animal's ability to supplement its natural resistance is its acquired host resistance.

If the animal has sufficient natural and acquired host resistance, it will overcome the disease and health will be regained. If the animal does not possess natural resistance and is unable to acquire resistance, death follows. If the natural resistance and the ability to acquire resistance are only present in a slight to a moderate degree, a chronic disease follows.

Streptomycin Plus Host Resistance

Experimental evidence indicated that one hundred per cent of the animals, which have been infected with tuberculosis a few weeks previously, could usually be saved when treated with therapeutic concentrations of streptomycin. Since these animals acquired some resistance to tuberculosis during the few weeks of infection prior to the administration of

streptomycin, it would be unfair to assume that these animals were saved by streptomycin alone. It would be more proper to assume that the animals had been saved by a combination of streptomycin and acquired host resistance.

Streptomycin Ineffective as Tuberculosis Therapy in Absence of Acquired Host Resistance

It has been established that streptomycin is rapidly absorbed in body fluids and normal tissues.[1-3] Being actively tuberculostatic, and possessing some bacteriocidal properties,[1-4] it might be expected that streptomycin would protect an animal against tuberculosis, that is, prevent the invasion of, and the progression of the disease.

Smith, Emmart and McCloskey[8] began intensive streptomycin therapy of guinea pigs on the same day of the tuberculous infection. They noted that there was little, if any evidence of therapeutic effect during the first four weeks of infection. The streptomycin did not check the invasiveness of the tubercle bacilli. It did not stop the progress of the disease. The streptomycin therapy did not prevent the tissue destruction associated with tuberculosis. Yet, during the following weeks of therapy, with no increase of dosage, a high degree of antibiotic effect was observed. All of the animals gained weight. Seventy per cent became tuberculin positive. Forty per cent became free of tuberculous lesions. All of the animals survived.

Similarly Steenken and Pratt[9] administered streptomycin to normal, healthy guinea pigs, but 48 hours prior to infecting them with highly virulent streptomycin sensitive tubercle bacilli. They concluded that streptomycin therapy did not prevent the early dissemination of the tubercle bacilli, nor did it prevent the progression of the tuberculosis. After the 27th day of infection, however, at which time the tuberculin test became positive, and caseation of the lesions occurred, the disease regressed, and all of the animals survived. Steenken and Pratt assumed that the positive tuberculin test and the caseation of the tuberculous lesions were evidence of acquired host resistance.

Only one human case has been found in the literature to be correlated with the animal experiments. Jones, Platt and Amil[10] reported a case of a thirty year old bacteriologist, who had injected a virulent strain of tubercle bacilli into her vein with suicidal intent. By the 15th day she had chills, a temperature of 104° and a sedimentation rate of 56 mm., but the roentgenograms of her chest remained normal, and her tuberculin test (first strength) was negative.

On the 21st day the roentgenogram of her chest showed generalized miliary infiltration. Streptomycin in 3 gram daily doses was administered, but the fever persisted, and the miliary lesions increased both in size and in number.

On the 26th day of infection the tuberculin test (2nd strength) became positive. The disease continued to progress and on the 40th day, the streptomycin was increased to 5 grams daily. By the 44th day the patient was suffering severe vertigo and there was no clinical improvement. The

streptomycin was reduced to 2 grams daily. Beginning on the following day (45th day of infection, 24th day of therapy) clinical improvement became rapid. By the 51st day (30th day of therapy) the temperature was normal. On the 59th day the roentgenogram showed the miliary lesions of the lungs to be static. By the 81st day (60th day of therapy) there was a definite improvement in the pulmonary lesions. On the 121st day (100th day of therapy) the patient was discharged home, and on the 200th day a roentgenogram of the chest showed no abnormality.

Discussion

In an attempt to correlate the course of early tuberculosis under intensive streptomycin therapy in the animal and in the human, the following facts can be pointed out:

In the first animal experiments, the tuberculous lesions in the presence of intensive streptomycin therapy developed and progressed for a period of four weeks, and then dramatically regressed with survival of all animals.

In the second animal experiments the animals were administered therapeutic doses of streptomycin 48 hours prior to infecting them with virulent tubercle bacilli as well as during the entire course of the experiment. Yet the tuberculous lesions developed and progressed during the first four weeks. After the tuberculin test became positive and the lesion became caseous, the lesions regressed, and all animals survived.

In the human case the tuberculosis progressed rapidly until the 45th day of infection in spite of 24 days of intensive streptomycin therapy. Then there followed a period of 66 days of less intensive streptomycin therapy during which time there was dramatic clinical improvement, and eventual roentgenographic disappearance of the pulmonary lesions.

In both the guinea pigs and in the human, there was a period of approximately four weeks during which time intensive streptomycin therapy was ineffective in preventing the invasion of tuberculosis[9] and the progression of tuberculosis.[8-10] After this period of four weeks, during which time the host was acquiring resistance against the tuberculosis, the streptomycin appeared to become very effective resulting in rapid regression of the disease. How much of the rapid regression of the tuberculosis is the result of the antibiotic and how much is due to the acquired host resistance is questionable. It appears that streptomycin and acquired host resistance supplement each other, but it is quite definite that streptomycin is an ineffective therapeutic agent against tuberculosis in the absence of acquired host resistance.

The fact that streptomycin, which is actively tuberculostatic and has some bacteriocidal properties, and which quickly reaches therapeutic levels in most of the body fluids and in normal tissues, failed to prevent the early invasiveness of the tubercle bacilli, and failed to check the progression of the disease, has brought forth the suggestion that early phagocytosis may prevent direct contact of the streptomycin with the micro-organism. It seems unreasonable, however, to believe that phagocytosis, an important part of host resistance, would cease after a four week period, thus exposing the micro-organisms to the potent antibiotic. It would appear to be

more logical to hold that host resistance represents a mobilization of the fighting forces of the body, and reaches a peak after an induction period of about four to six weeks. It then follows that streptomycin becomes much more effective and potent when supplemented by strong host resistance.

If the premise is true that streptomycin is ineffective prior to the acquiring of host resistance, and is effective in its presence, some of the limitations of streptomycin are more easily understood. It follows that any measure which might accelerate or increase host resistance, would supplement the streptomycin therapy of tuberculosis, increasing its effectiveness. The following methods for accelerating and increasing acquired host resistance are suggested:

A supportive diet including adequate vitamins, protein, calcium and minerals.

Mild exercise interspersed with adequate rest, in order to maintain all organic functions of the body in the best physiological state.

Early administration of streptomycin in combination with other antituberculous agents, in order to take advantage of host resistance as soon as it is acquired.

When indicated, small daily doses of thyroid extract to increase basal metabolism to normal or slightly above.

When indicated, a schedule of gradually increasing doses of tuberculous antigens (tuberculin) injected intradermally at many different sites, in order to increase antibody response.

CONCLUSIONS

It is concluded from the above observations that streptomycin is ineffective in the treatment of tuberculosis prior to the acquiring of host resistance, but becomes effective as soon as acquired host resistance becomes well established.

Methods of accelerating and increasing acquired host resistance have been suggested as a means of enhancing the effectiveness of streptomycin therapy in tuberculosis. It is also possible that similar methods of accelerating and increasing host resistance could enhance the effectiveness of other antibiotic and chemotherapeutic agents in the treatment of tuberculosis, and even some other diseases.

CONCLUSIONES

De las observaciones arriba relatadas se concluye que la estreptomicina no es efectiva si se usa en la tuberculosis antes de que el huésped haya desarrollado resistencia a la enfermedad, pero se hace efectiva tan pronto como el huésped tiene resistencia bien establecida.

Lost métodos para acelerar la adquisición de la resistencia del huésped se han sugerido como un medio de aumentar la efectividad de la estreptomicina para tratar la tuberculosis. También es posible que otros métodos similares sean capaces de aumentar la efectividad de otros antibióticos y quimioterápicos en el tratamiento de la tuberculosis y aún de otras enfermedades.

RESUME

L'auteur conclut des observations ci-dessus que la streptomycine est inefficace dans le traitement de la tuberculose avant que le porteur de bacilles n'ait acquis un terrain résistant et devient efficace dès que cette résistance est nettement obtenue.

Des méthodes propres à accélérer et augmenter la résistance à l'infection sont proposées comme moyen d'élever l'efficacité de la thérapeutique par la streptomycine en tuberculose. Il est également possible que de telles méthodes accélèrant et augmentant la résistance à l'infection puissent élever l'efficacité d'autres agents antibiotiques et chimiothérapiques dans le traitement de la tuberculose, et même dans certaines autres affections.

SCHLUSSFOLGERUNGEN

Es wird aus den oben wiedergegebenen Beobachtungen der Schluss gezogen, dass Streptomycin bei der Behandlung der Tuberkulose unwirksam ist, bevor es zu einer erworbenen Resistenz des Trägers gekommen ist, dass es jedoch wirksam wird, sobald sich die erworbene Resistenz des Trägers voll entwickelt.

Es wurden Methoden empfohlen zur Beschleunigung und Steigerung der erworbenen Trägerresistenz als einem Verfahren zur Erhöhung der Wirksamkeit der Streptomycin-Therapie bei der Tuberkulose. Es ist ebenfalls möglich, dass ähnliche Methoden der Beschleunigung und Steigerung der Träger-Resistenz die Wirksamkeit von anderen Antibiotizis und chemotherapeutischen Stoffen bei der Behandlung der Tuberkulose und sogar einiger anderer Krankheiten erhöhen könnte.

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Rheumatic Heart Disease in East Pakistan

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Introduction

Since the beginning of this century rheumatic fever has been studied more thoroughly and various theories have been postulated, ascribing the disease to non-specific streptococcal infection,[1] allergic to non-specific allergen[2], virus hypothesis[3], and streptococcal beta-haemolyticus infection with abnormal antigen-antibody response.[4, 5, 6]

With advance in the field of bacteriological investigations, especially those of Lancefield and Griffith, it is now apparent that epidemiology of rheumatic fever is related closely to the incidence of preceding streptococcal illness. More informative and interesting researches have been made recently by Rammelkamp and others,[7] in their studies on "the Epidemiology of Rheumatic Fever in Armed Services." The variation in the incidence of rheumatic fever in these studies has been shown to be independent of season, and indicated to have little direct effect of altitude, climate or humidity. They conclude that overcrowding, dampness, economic factors, effect the incidence of rheumatic fever only because they are related to the incidence of streptococcal infection in general. Why a certain section of the population under similar environmental condition suffers from rheumatic fever has not yet been settled excepting the indication that "host factor" plays a significant role either by their susceptibility or by their exaggerated antibody response.

In the field of experimental medicine recent works of Murphy and his colleagues[8] denotes a great advance in the pathogenesis of rheumatic fever. At last myocardial Aschoff bodies have been produced in rabbits after focal cutaneous infection with group A streptococci. Exaggerated antistreptococcal antibodies (antistreptalysin O) have been noted in their blood, and in addition an interesting observation on the hypertrophy of adrenal cortices with histopathological changes has been observed. The peculiarity of host factor has once more been substantiated by the experimental method.

However no proper study of rheumatic fever has been done in tropical countries. Price[9] avoids the subject by stating that it is more prevalent in temperate and humid climate than in others. Boyd[10] states "in the tropics, where Haemolytic streptococci are rarely found in the throat, scarlet fever is unknown and rheumatic fever is very uncommon." Paul White[11] says "permanent residence in the tropics is preferable if a 'rheumatic family' can readily arrange it."

In "The Symposium of Rheumatic Fever" edited by Thomas Lewis in which the subject has been dealt with exhaustively, it has been asserted that this disease is "rare in the tropical countries" but as the autopsy record on the people of Guam during World War II by Zimmerman showed

pathological evidence of old rheumatic heart disease in many cases, it has been concluded that rheumatic fever was unrecognised as a clinical entity.

Factors which are so far known to contribute to the causation of rheumatic fever are all present in a tropical country like East Pakistan. Its geographical conditions are described below:

Eastern Pakistan is situated between 20°75′ and 26°75′ North latitude and 88-92.4° East longitude. Its capital Dacca is exactly 90°E. of Greenwich.[12] Nearly the whole of the province belongs to one natural region —the lower Ganges Valley or Deltas Region. It consists of the vast alluvial plain of the deltas of the mighty rivers, the Ganges and the Brahmaputra, which originate in the Himalayas to the north and flow into the Bay of Bengal in the south. Thus the major part of the country is traversed by the rivers and rivulets which remains inundated about four to five months during the rainy season (Wet Summer).

The tropic of cancer bisects the province (passing through the District of Dacca) and the climate is therefore tropical.[13] There is a wide variation of temperature in different parts of the country, the southern part being characterized by double maximum temperature up to 100°-105°F. with an average temperature 95°-90°F. whereas the coastal areas veering around 80°F. The year has been divided into four seasons. Winter (December to February), Dry Summer (March to May), Wet Summer (June to September) Autumn (October and November) according to temperature and rainfall.

The rainfall varies from 60″-120″. Because of heavy rainfall the country is always green and does not dry up. The humidity of the place is high ranging from 70 to 98 per cent; thus the climate is mostly damp.

Eastern Pakistan has a population of 41,932,329 with an area of 54,141 sq. miles, the density of the population to square miles amounts to 774 in general but owing to its peculiar geographical condition the concentration of population is highest around active rivers. This forms two belts of thickly populated areas, where the density varies from 1000-1500 per sq. mile as shown in the map. The people of East Pakistan are mostly agrarian, economically backward and generally live on joint family system.

Considering these climatic conditions, it would have been surprising if the disease had not been prevalent in this country. Low socio-economic conditions among the masses both in urban and rural areas, overcrowding, bad hygienic and insanitary conditions are common. Climatic condition favourable to the growth of bacteria, persists in the environment and soil throughout the whole year. Naturally and logically sore throat, tonsillitis and upper respiratory tract infections, mostly of group A. streptococcal origin are not infrequent among the children. This throat condition along with enlargement of the tonsillar glands, if considered together would be found in nearly 75 per cent of children and adolescent groups. The above conditions are contributory to causation of rheumatic condition and as a matter of fact in the author's experience, rheumatic heart disease is common, producing a complicated social problem for this country which is still too young to have proper rehabilitation or cardiac centres. The

same view is held by Drs. D. N. De, J. C. Banerjee and A. K. M. Abdul Wahed, Professors of Medicine in Calcutta and Dacca Medical Colleges. The latter always taught that "Rheumatic fever is as common in Bengal as in other parts of the world where its incidence is frequent."

Clinical Materials

The author as one of the consulting physicians had opportunity to study rheumatic fever in a general ward of Dacca Medical College Hospital, the only organised institution of the country with a population of 42 millions. The criteria of admission was the urgency of the patients' condition rather than any special disease. Therefore cases such as typhoid fever, acute malaria, kala-azar, pneumonia, cerebral thrombosis, gastro-duodenal ulcers, Hodgkin's disease, etc., used to get admission in preference to chronic rheumatic heart disease. Acute rheumatic fever and congestive cardiac failure not infrequently come to the ward as acute cases. Occasionally, of course, chronic rheumatic carditis with mitral and aortic valvular diseases were admitted when the wards were not congested. In the course of five years from January, 1949 to December, 1953, the total number of patients admitted in the Medical Wards was 19,011 of which acute rheumatic fever and rheumatic heart disease were 606. Other particulars of these cases are detailed below and in Tables I to IV, and given in the appendix.

Analysis of Cases

(1) Total number of patients	606
A. Acute rheumatic fever	85
B. Chronic rheumatic carditis	521
(a) Mitral valvular lesions	486
(b) Aortic and mitral valvular lesions	24
(c) Aortic valvular lesions	11
(2) Age group vide Table I	
(3) Sex—Male	403
Female	203
(4) Complications:	
(a) Auricular fibrillation	94
(b) Congestive cardiac failure	262
(c) Sub-acute bacterial endocarditis	11
(d) Pulmonary infarct	13
(e) Cerebral embolism	4

Investigations

As a routine the following investigations were done in each case:

(a) Clinical history including past history, family history and personal history.

(b) Haemoglobin, red blood cell count, white blood cell count with differential.

(c) Sedimentation rate.

(d) Skiagram of chest in different views.
(e) Screening with barium swallow.
(f) Electrocardiogram whenever possible.
(g) Examination of urine, stool and sputum.
(h) Throat swab examination especially if the case was acute.
(i) Blood culture in acute and febrile cases.
(j) Other special examinations as indicated including photographic records of rheumatic carditis with valvular lesions, skiagrams and necropsies.

Clinical Features:

Patients presented themselves with different clinical pictures:

(1) The commonest form was sudden febrile onset in young person, of age group 5 to 15 years, associated with pain and swelling of ankle and knee joints of one side or other. The attack then migrated to the next group of joints as wrist, hip, and shoulder within 48 to 72 hours. By the time the second group of joints were involved, the first group thus constituting a typical flitting polyarthritis. If patients were outside the hospital more than a week they usually received antimalarial and antityphoid treatment without benefit. Clinical examination revealed pallor and tachycardia out of proportion to fever. Occasionally rheumatic nodules were demonstrable. Examination of the heart revealed diffuse pulsation over

TABLE I—AGE GROUPING OF CASES OF RHEUMATIC HEART DISEASE IN EAST PAKISTAN

Age Group	Total No. of Cases	Per Cent
1 - 5	1	0.1
6 - 10	26	4.3
11 - 15	94	15.2
16 - 20	116	19.2
21 - 25	85	14.0
26 - 30	84	13.9
31 - 35	55	9.1
36 - 40	37	6.2
41 - 45	29	4.8
46 - 50	27	4.5
51 - 55	22	3.6
56 - 60	19	3.2
61 - 65	7	1.2
66 - over	4	0.7
	606 cases	100.0

the apex with a soft first sound and associated with a systolic murmur and in some cases a diastolic murmur. Examination of the throat occasionally revealed congestion or obvious tonsillitis but frequently tonsillar glands were enlarged.

(2) *Insidious onset:* Young adult of age group 16-25 years, presented with the history of breathlessness on normal exertion, gradually becoming worse in the course of three to six months without previous attacks of acute rheumatic fever. Clinical examination revealed signs of mitral stenosis in the heart with its typical presystolic thrill and rumbling diastolic murmur, ending in accentuated first heart sound.

(3) Women of child bearing age (25 to 40); mother of two or three children; complained of attacks of breathlessness from fifth or sixth month of pregnancy. Previous pregnancies were uneventful. Clinical examination revealed typical mitral stenosis. There might have been a history of arthritis of a flitting nature, in childhood or adolescence but there was no adverse episode during this long interval till the present attack.

(4) Elderly men and women aged 40 to 45 presenting with obvious signs and symptoms of congestive cardiac failure. There might be no past history of acute rheumatic fever. Clinical examination revealed auricular fibrillation, marked enlargement of heart with valvular lesions, usually both mitral and aortic.

(5) Fairly active young men suddenly having haemoptysis reported to the tuberculosis clinic, and subsequently referred back as non-tuberculous

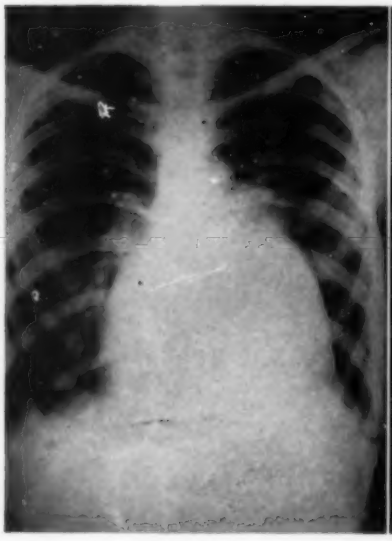

FIGURE 1

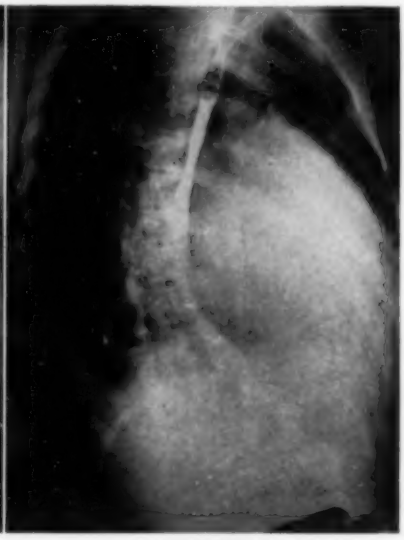

FIGURE 2

Figures 1 and 2 (Case 2): A case of rheumatic carditis with cardiac failure, initial stenosis.

TABLE II—TYPES OF LESIONS

	No. of Cases	Per Cent
1. Acute rheumatic fever	85	14
2. Mitral stenosis	480	79.2
3. Mitral valvular & aortic lesions	24	4.0
4. Aortic incompetence	9	1.5
5. Mitral incompetence	6	1.0
6. Aortic stenosis	2	0.3
	606	100.0

haemoptysis to the general hospital. Clinical examination showed it to be a typical case of mitral stenosis.

(6) Young men with obvious dyspnoea of recent origin. Clinical examination revealed typical carotid pulsation, water-hammer pulse and enlarged heart with signs of aortic incompetence. Not infrequently these cases presented themselves with history of cardiac asthma.

(7) Occasionally adult patients reported with symptoms of hemiplegia of sudden onset. Clinical investigations revealed the cases to be rheumatic carditis with mitral valvular lesion, having cerebral embolism.

(8) Occasionally patients have been sent to a hospital as cases of kala-azar or typhoid fever because of continued fever with splenomegaly. Clinical examination and investigations disclosed the cases to be subacute bacterial endocarditis in rheumatic carditis.

Associated Diseases and Conditions

Since East Pakistan is still an underdeveloped country, it has some preventable and endemic diseases prevalent throughout the year, with periodic increase in their intensities. Malaria, kala-azar, typhoid group of fevers, dysenteries, influenza and common cold, infectious fevers such as measles, smallpox and chickenpox, diphtheria, cerebrospinal fever, helminthiasis and specially ankylostomiasis are common. The last is one of the most common causes of severe anaemia in the mass population of

TABLE III—COMPLICATIONS OF 606 CASES

		Total	Per Cent
1. Auricular fibrillation		94	15.2
2. Congestive cardiac failure		262	43.2
3. Subacute bacterial endocarditis		11	1.8
4. Embolism	Pulmonary	13	2.1
	Cerebral	4	0.7
5. Heart block		8	1.3
		392	64.3

the country. Of course all other conditions enumerated above cause a condition of low vitality and anaemia among people. Tuberculosis in itself is another serious problem for this society.

Rheumatic heart diseases cause incapacity quicker among this population. Cardiac reserve is lost early and congestive failure sets in comparatively rapidly. The convalescence becomes more protracted and cardiac failure recurs during convalescence. The reasons are obvious. Even without organic heart disease many persons suffer from anaemia, hypoprotienemia and congestive cardiac failure following ankylostomiasis, chronic malaria and kala-azar even when these conditions are controlled with specific therapeutic measures. What happens is that owing to their diverse socio-economic condition, the majority is in a state of malnutrition. Few people can afford to have proper rest and treatment or extra nourishment with antianaemic factors during convalescence and not infrequently they are obliged to undertake exertion prematurely.

Management

Acute rheumatic fever cases are put on sodium salicylate 150 to 200 grain in adult and proportionate dose according to the age, and the response is often dramatic within 47 hours. This response is also considered as diagnostic of rheumatic fever. If it is not as satisfactory as expected, the diagnosis is either reviewed or more often careful clinical examination reveals some complications as pericarditis, pneumonia or other associated conditions. Almost always antianaemic treatment is required simultaneously as iron, acid and liver extract in tropical macrocytic anaemia. Antibiotic and chemotherapeutic drugs are used whenever there is

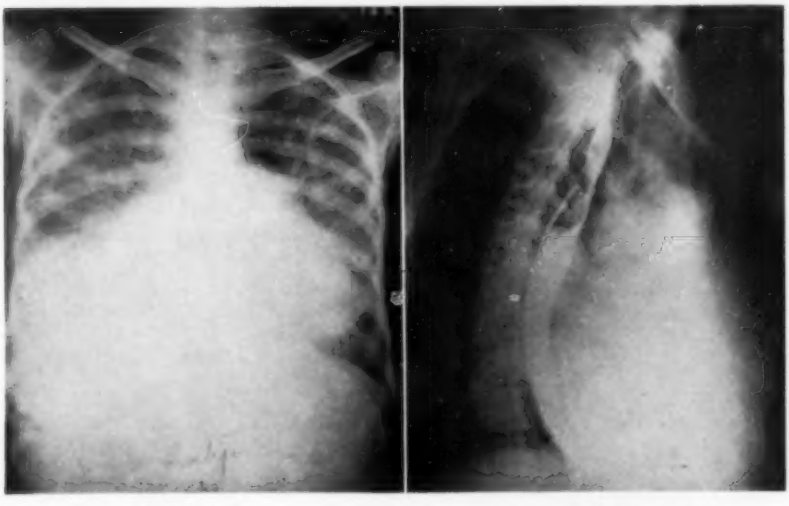

FIGURE 3 FIGURE 4

Figures 3 and 4 (Case 3): A case of mitral stenosis.

sign of infection especially in the throat. In case of cardiac failure, digitalis preparations are used. In those cases which are not responsive to digitalis or the progress is stationary, especially with normal pulse rate, mercurial diuretics are used with beneficial response. Sleeping pulse rate, temperature and sedimentation rate are recorded regularly to assess the progress and activity of the condition. Cortisone and ACTH have been used for the last few months with good results in acute cases but the number is too limited to be of any statistical value.

APPENDIX I—ILLUSTRATIVE CASE RECORDS

Case 1: Miss S. B., a 15 year old student was admitted to the hospital on March 4, 1950 with 10 days' history of fever with flitting polyarthritis affecting ankles, knees, elbows and wrists in that order. She had an attack of tonsillitis two weeks previous to the onset of the present complaints.

Family history: Parents living and healthy. She had four elder brothers and one younger sister. The second brother was undergoing domiciliary treatment for pulmonary tuberculosis.

Physical examination disclosed a fairly well nourished moderately built, anxious looking girl. She was markedly pale and her temperature was 102 degrees F. Pulse 124, respiration 36. Her wrist and elbow joints were red, swollen and tender with all movements restricted and painful. Few tender nodules could be palpated around knee and ankle joints although there was no evident swelling. Examination of the heart revealed only tachycardia. Other systemic examinations revealed no abnormality.

Investigations: Haemoglobin 70 per cent, red blood cells 2.5 millions, white blood cell count 5800 with normal differential count. Sedimentation rate 92 mm. per hour. Throat swab did not show growth of Streptococcus haemolyticus on repeated examinations. Skiagram of chest was normal.

Management: She was put on sodium salicylate 120 grains daily for three days and the response was satisfactory. She became afebrile within 48 hours. Her pain and swelling of joints subsided, the sedimentation rate came down to 30 mm. on the fifth day. The dose of salicylate was reduced and she was kept in the hospital for six weeks with general and antianaemic treatment.

Case 2: B. Z., a 20 year old village farmer reported to the out-patient department on January 6, 1953 with chief complaint of exertional dyspnoea of six months duration. Past history and family history were non-contributory. Physical examination revealed a malnourished, moderately built young man without evident dyspnoea. Examination of the heart showed apical impulse on the fifth space, on left midclavicular line with presystolic thrill. The first sound at the mitral area was accentuated and preceded by a rumbling crescendo murmur. Other systemic examination was normal. There was no sign of activity, his pulse rate was 80 per minute and sedimentation rate 12 mm. per hour. Fluoroscopy and skiagram showed typical mitralisation of the left border (Fig. 1) and displacement of the oesophagus by enlarged left auricle with barium swallow in the right anterior oblique position (Fig. 2).

During his six weeks' hospitalization he had no episode of dyspnoea and he was discharged to attend out-patient department for any recurrence.

Case 3: A. G., a muslim woman aged 30 years, wife of a village school master was admitted to the hospital on February 2, 1953 with one months' history of palpitation, breathlessness and occasional oedema of legs. She was five months pregnant. Her previous three pregnancies and confinements were uneventful. All the children were

TABLE IV—SEX INCIDENCE

Sex	No. of Incidence	Per Cent
1. Male	403	66.5
2. Female	203	33.5
TOTAL	606	100.0

fairly healthy. She admitted having suffered from fever with flitting polyarthritis when she was 10 years old. Her family history suggested that her father died of congestive cardiac failure and her mother and only brother were subjects of rheumatism. Physical examination revealed her to be moderately nourished, anaemic with evident oedema of feet and legs. Her temperature was 98 degrees F. Pulse 100, respiration 30. She did not show prominent neck veins or enlargement of liver but examination of her heart revealed moderate enlargement with soft first sound partly replaced by a harsh systolic murmur and a long mid-diastolic murmur. Pulmonary second sound was accentuated and reduplicated. Skiagram of chest showed typical mitralisation of the heart with enlarged left atrium in the right anterior oblique view (Figs. 3 and 4). She was asymptomatic with rest, general and antianaemic treatment. She was transferred to the maternity ward to consider sterilization after confinement. Cardiogram showed: Right sided hypertrophy. Prominent P in limb leads and S is almost absent in V_1.

Case 4: A. C., a Hindu man aged 43 years, a jute dealer, was admitted to the hospital in congestive cardiac failure. He dated his symptoms of breathlessness and occasional oedema of feet from the age of 30 for which he had to be hospitalized twice during the last three years. There was a past history of rheumatic fever at the age of 15 years.

Physical examination revealed a fairly well nourished man with evident dyspnoea, prominent neck veins and oedema of both feet, legs, thighs and genitalia. Pulse was 118 and respirations were 30 per minute. The temperature was normal. Examination of the heart showed considerable cardiac enlargement with a heaving apical impulse at the sixth space in the left anterior axillary line. The mitral first sound was replaced by a systolic murmur. The second sound was indistinct and followed by a mid-diastolic murmur. In the aortic area there were a short systolic and a blowing diastolic murmur. Blood pressure was 115/70. Abdominal examination revealed ascites, and enlarged and tender liver extending four fingers breadth below the right costal margin. There was basal congestion of both lungs. X-ray film of the chest showed marked enlargement of heart. Fluoroscopy revealed enlargement of the left atrium and moderate enlargement of both right and left ventricles.

Case 5: A. T., aged 20 years, a businessman attended the tuberculosis clinic for sudden haemoptysis while coming back from his office on the previous evening.

Past history, family history: Non-contributory. He was referred from the clinic with the note "Non-tubercular haemoptysis."

Physical examination disclosed a thin young man with moderate anaemia. Temperature normal. Pulse 100 and respirations 20 per minute.

Examination of the heart revealed typical presystolic thrill, rumbling presystolic murmur ending in the accentuated first sound over the mitral area. Pulmonary second sound was accentuated. Blood pressure 110/80 mm. of Hg.

Investigations: Haemoglobin 65 per cent, red blood cells 3.1 million with normal differential count. Erythrocytic sedimentation rate 10 mm. Fluoroscopy and skiagram of the chest confirmed presence of mitral stenosis. Routine examination of stool showed ova of ankylostoma.

Management: He was kept under observation for 3 weeks. There was no sign of activity of rheumatic infection. Pulse became normal on rest and remained between 72 and 80. Antihelminthic and antianaemic treatment were given and he was released from hospital to attend out-patient department.

Case 6: M. M., aged 40 years, shopkeeper, was admitted on September 2, 1952 with history of palpitation and nocturnal dyspnoea of one months' duration. He admitted exertional dyspnoea for about six months.

Past history of rheumatic fever at the age of 13 and 20 years. His wife and four children are healthy. Physical examination revealed a thinly built, fairly well-nourished, dyspnoeic man. He showed typical carotid pulsation and water-hammer pulse, 110 per minute. Blood pressure was 140 systolic and 40 diastolic.

Heart was enlarged with heaving apical impulse on the sixth space in left anterior axillary line. There was a soft blowing diastolic murmur on the aortic area and a systolic murmur in the mitral area. There were scattered rhonchi over both lungs with a few moist rales at the left base.

Skiagram showed marked enlargement of the left ventricle with prominent aortic knuckle. Cardiogram showed: Left ventricular hypertrophy. Chest leads showing diminutive R waves with deep S waves in V_1 V_2 V_3 and V_4.

Investigations: Haemoglobin 60 per cent, red blood cell three million, sedimentation rate 20 mm. per hour. Wassermann and Kahn tests were negative.

Management: He improved on general treatment and was released with the advice of avoiding over-exertion. He has not had nocturnal dyspnoea for the last year, although he has become a subject of palpitation with slight anxiety.

Case 7: A. R., aged 25 years, the son of a businessman, was admitted on December 4, 1953 with irregular fever for two months, not responding to ordinary chemotherapeutics and antibiotics.

Clinical examination revealed an emaciated anaemic young man. There was moderate degree of clubbing of fingers and toes. Temperature 101 degrees F. Pulse 132, respiration 36 per minute.

There were carotid and brachial pulsations. Examination of the heart showed evidence of mitral and aortic valvular lesion. His spleen was enlarged two fingers breadth below the costal margin, and was soft.

Investigations: Haemoglobin 65 per cent, red blood cells 2.2 million, white blood cell count 8000 c.mm., neutrophils 65 per cent, lymphocytes 25 per cent, monocytes 10 per cent, eosinophiles 5 per cent, sedimentation rate 110 per hour. Urine showed trace of albumin with definite microscopical red blood cells without casts. Blood culture was positive to Streptococcus viridians on repeated examinations. Skiagram in recumbent position showed enlarged heart with mitralisation.

Progress: He responded to massive doses of penicillin and supportive treatment and became afebrile after 10 days when suddenly he had haemoptysis with pain in right side of the chest, due to pulmonary infarction from left leg which showed evidence of phlebo-thrombosis. He expired 48 hours after this episode following sudden dyspnoea possibly from massive pulmonary embolism. Autopsy was not allowed.

Case 8: Miss M. K., aged 14 years, was admitted on December 11, 1953 with the history of paralysis of right half of body following sudden unconsciousness while carrying a water jar from the neighbouring pond.

Clinical examination disclosed right-sided hemiplegia with increased deep reflexes and extensor planter response on the affected side.

Examination of the heart revealed a typical presystolic murmur in the mitral area ending in accentuated first sound. There was history of rheumatic carditis in the family. One of her brothers was undergoing treatment for congestive cardiac failure with mitral and aortic valvular lesions in the same hospital.

Case 9: B. Z., aged 16 years, a cowboy was admitted to the hospital on December 28, 1953 with congestive cardiac failure of one month's duration. He gave a history of rheumatic fever when he was eight years old and exertional dyspnoea for six months. On physical examination he was orthopnic, cyanosed and looked exhausted. His neck veins were prominent and pulsatile, and he had oedema of the inferior extremities, abdominal wall and both hands. There was ascites with tender enlarged liver to the level of umbilicus. Examination of the heart revealed bulging of the precordium with diffuse pulsation. Apical impulse was visible at the sixth left space in the anterior axillary line. The first sound in the mitral area was replaced by a systolic murmur and there was a long diastolic murmur. The aortic area revealed a rough systolic murmur conducted upward along the neck. Cardiac rhythm was irregular. Pulse 100, irregularly irregular, low volume and tension, blood pressure, 112/30. Moist rales were heard over lung bases.

Progress: He did not respond to treatment and died after three days.

Partial autopsy was allowed. The heart was enlarged; there was mitral stenosis. Histopathological section of the cardiac muscles showed degeneration with formation of Aschoff's nodule. Liver showed centrilobular necrosis.

Case 10: N. A., aged 45, a fisherman, was brought to the emergency department on February 5, 1953 with asthma. He gave a history of attacks of paroxysmal nocturnal dyspnoea for three years, specially during winter. For the last six months, his attacks became more frequent and he admitted dyspnoea and palpitation on accustomed exertion during day also. A week prior to his visit he fainted on the boat while fishing and since then he had continuous asthmatic attacks. Past history did not reveal acute rheumatic fever, neither was there venereal disease. Clinical examination revealed typical signs of left ventricular failure. His heart was enlarged; the apex beat was at the left seventh intercostal space in the anterior axillary line with a heaving impulse. Auscultation of the heart disclosed a rough systolic and a blowing diastolic murmur in the aortic area with a soft systolic murmur in the mitral area. His lungs were full of bubbling rales. Blood pressure 150/70 mm. Hg. The pulse was 130/min. and respirations were 40 per min.

Investigations: Haemoglobin 35 per cent. Red blood cells 1.8 m/c.mm. Skiagram of the chest showed marked enlargement of the left ventricle with a prominent aortic knuckle. He expired within 12 hours of admission in the hospital.

Partial autopsy was allowed. Heart was enlarged with marked hypertrophy of the left ventricle. Aortic valves were thick and rough showing evidence of old vegetation. Microscopical examination of the cardiac muscle showed typical Aschoff's nodules.

SUMMARY

In East Pakistan no previous study had been made of the incidence of rheumatic fever and rheumatic carditis. The present study, although of short duration of five years, proved definitely that this disease is significantly prevalent in this part of the world. It has been shown in this paper that the factors so far known to contribute to the causation of rheumatic fever are definitely prevalent in this country. Its geographical condition, climate, socio-economic condition, and prevalence of streptococcal infection are as marked as any other country where rheumatic fever is already known to be prevalent.

Acknowledgements: I gratefully acknowledge the assistance of Dr. M. Hassan, Curator of Pathology department and Dr. Shamsul Huq, my clinical assistant for their invaluable help in preparation of this paper. My thanks are due to Mr. Musa Chunara, student of Medical College for his photographic work. I am really thankful to Col. T. D. Ahmed, Surgeon-General with the Government of East Pakistan for his valuable guidance. I also thank Dr. A. K. M. Abdul Wahed, Principal-cum-Superintendent, Dacca Medical College & Hospital for his permission to publish this paper.

RESUMEN

En el Pakistan Oriental no se había hecho antes un estudio sobre la incidencia de la fiebre reumática y la carditis reumática.

El estudio presente, aunque de corta duración de cinco años, demostró claramente que esta enfermedad prevalece con significación en esta región del Mundo.

Se ha mostrado en este trabajo que los factores hasta ahora conocidos como contribuyentes para causar la fiebre reumática definidamente, prevalecen en este País. Sus condiciones geográficas, clima, situación socioeconómica, y prevalencia de la infección de estreptococos son tan marcadas como en cualquiera otro país donde la fiebre reumática se sabe que prevalece.

RESUME

Dans l'Est du Pakistan, il l'existe jusqu'à présent aucune étude sur la fréquence du rhumatisme articulaire et du rhumatisme cardiaque. L'étude actuelle, bien que portant sur une courte période de cinq années, a apporté la preuve certaine que cette affection est particulièrement fréquente dans cette partie du monde. L'auteur montre dans cet article que les facteurs considérés comme susceptibles de contribuer à l'apparition du rhumatisme cardiaque sont prédominants dans cette région. Son état géographique, climatique, ses conditions socio-économiques, et la fréquence des infections streptococciques sont aussi nets que dans toute autre région où le rhumatisme articulaire est connu pour être souvent rencontré.

ZUSAMMENFASSUNG

In Ostpakistan ist zuvor noch keine Untersuchung angestellt worden über die Häufigkeit des rheumatischen Fiebers und der rheumatischen Karditis. Die vorliegende Untersuchung, obwohl nur den kurzen Zeitraum von 5 Jahren umfassend, ergab eindeutig, dass diese Krankheit von beträchtlicher Häufigkeit ist in diesem Teil der Welt. Es ist in dieser Ver-

öffentlichung dargelegt worden, dass die bisher bekannten Faktoren, die zu der Entstehung des rheumatischen Fiebers beitragen, in diesem Land eindeutig vorherrschen. Dessen geographische Umstände, die klimatischen, soziologischen Faktoren und das Vorkommen von Streptokokken-Infektionen sind in der gleichen Weise ausgeprägt wie in irgend einem anderen Land, von dem das Auftreten des rheumatischen Fiebers bereits bekannt ist.

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The Surgical Treatment of Cavitary and Non-Cavitary Tuberculosis in the Non-Infectious Patient

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The excellent results of chemotherapy in the current management of pulmonary tuberculosis require a critical evaluation of the role of surgery in this disease.[1] As the employment of antituberculous drugs continues to reverse the infectious state of greater numbers of patients, the goal of today's treatment is more often the prevention of future relapse than the immediate control of active tuberculosis. To advocate a policy of surgical prophylaxis for the non-infectious patient with a closed or open lesion, it must first be apparent that the incidence of clinical relapse is significantly greater in a carefully studied series of medical patients than in a parallel surgical group.

The present report* is concerned with the medical and surgical results in patients presenting either closed or open lesions following six to eight months of antituberculous chemotherapy. Each patient in this study had had sputum negative for tubercle bacilli by culture for at least three consecutive months prior to the stated observation point.

Non-Cavitary Group (Closed Negatives)

There were 226 patients who achieved the closed negative state on original chemotherapy; of these 90 were resected and 136 were not resected.[2] This was not a randomized program and indications for resection were drawn largely on an empirical basis in a effort to improve an already favorable outlook.

Indications for Resection (Table I)

All suspected tuberculomas are removed for reasons of both diagnosis and treatment. In addition, surgery is considered to be indicated when there has been x-ray film instability or unfavorable change in the lesion, with or without specific therapy.

Pulmonary "coin" lesions are resected because of their indeterminate nature and the ever present possibility of malignancy particularly in the older age group.

Dense lesions, probably conglomerate caseous foci, which measure 3 cm. or more in diameter are recommended for excision, especially if they are discrete and require removal of minimal lung tissue.

Resection is advised in patients exhibiting resistant organisms to one or more drugs before sputum conversion. Excision is also suggested when a patient manifests intolerance to at least two of the major drugs.

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*From the Veterans Administration Hospital, Sunmount, New York.

TABLE I
INDICATIONS FOR RESECTION CLOSED (NON-CAVITARY) LESIONS

1 Tuberculoma {diagnosis uncertain / instability
2 Solitary dense lesion, 3 cm. or more in diameter
3 Resistant tubercle bacilli
4 Drug intolerance (two or more)
5 Systemic disease or constitutional factors
6 Economic reasons
7 Retreatment candidate with evidence of previous x-ray or bacty relapse
8 Localized residual in area of damaged lung
9 Cavity at onset of treatment?
10 Active tuberculous bronchial disease?

In those with residual closed lesions who, because of "constitutional inadequacy," psychopathic personality, alcoholism, systemic disease such as diabetes, age, sex, race or other factors that affect the prognosis, and who, because of these preceding qualities, will not follow a recommended medical regimen, or are not amenable to further medical supervision, resection is recommended.

Those who have been brought to the observation point on a retreatment drug program and have prior evidence of x-ray film instability or bacteriological relapse are advised to have resection.

Patients with evidence of residual closed tuberculous lesions in a lobe with concomitant bronchial deformity or emphysematous changes are advised to have resection surgery.[3]

Results

The cumulative relapse rate for the closed negative group has been calculated by the "Life Table" method up to five years after the observation point (Table II).

In this study, relapse has been rather strictly defined as either a smear or cuture positive for acid fast bacilli or unfavorable change by x-ray film.

Among the resected group (90 cases) relapse occurred in eight (nine per cent). The relapses consisted of isolated positive sputum or gastric cutures in all but two cases, who had both x-ray film and bacteriologic relapse reuiring retreatment. One had a postresection reactivation of disease in the operative site of a wedge resection. Secondary resection was successful in arresting the activity. The remaining surgical morbidity was non-tuberculous and consisted largely of various space problems which were treated by transient intercostal closed drainage.[4] There was no

TABLE II
RESULTS IN 226 NON-CAVITARY (CLOSED) NEGATIVE PATIENTS

	No. Pts.	Relapse	No Cavity Onset Treatment	Cavity Onset Treatment
Non-Resected	136	19 (14%)	12/120 (10%)	12/60 (20%)
Resected	90	8 (9%)	10/120 (9%)	5/46 (11%)

operative mortality and no case died of tuberculosis within the period of follow-up. All other "relapses" became inactive again and have been followed 20 to 30 months without further evidence of tuberculous activity.

In the 136 patients closed negative at the observation point and not resected, relapse was more frequent (14 per cent). There was no death from tuberculosis but these relapses were generally of considerable consequence: six patients had both x-ray film and bacteriologic relapse requiring retreatment and two others required prolonged retreatment for new or reactivated extra-pulmonary foci. Only three remained active at the time of our most recent follow-up, three had died of non-tuberculous causes and the remainder had regained the inactive state.

Of considerable interest is the further subdivision of the patients with closed lesions into those exhibiting cavity at the onset of treatment and those in whom cavity was absent or indefinite. Of those without cavity 10 of 120 (9 per cent) relapsed with no significant difference between the resected and non-resected groups. However, of those who had cavity prior to chemotherapy, 17 of 106 (16 per cent) relapsed. If this group is further broken down, five of 46 (11 per cent) of resected cases relapsed while 12 of 60 (20 per cent) of the non-resected cases relapsed.

Comment

While there is no significant difference in the relapse incidence of resected and non-resected closed negative groups which cannot be accounted for by such background factors as extent and distribution of disease, the disparity between those patients with and without demonstrable cavity at the onset of treatment is important.

Previous investigations have indicated that the danger of residual non-cavitary lesion is inherent in its bacillary content.[5, 6] In a bacteriological study of resected material from these closed negative patients, tubercle bacilli were recovered in 20 per cent by culture or guinea pig inoculation.[7] However it may be recalled that the majority of these lesions were removed after the patient had received four to six months of chemotherapy. It may be argued that if the healing process was allowed to continue under the influence of 12 to 18 months of drugs, the incidence of recoverability for bacilli would be in the realm of 5 to 10 per cent.

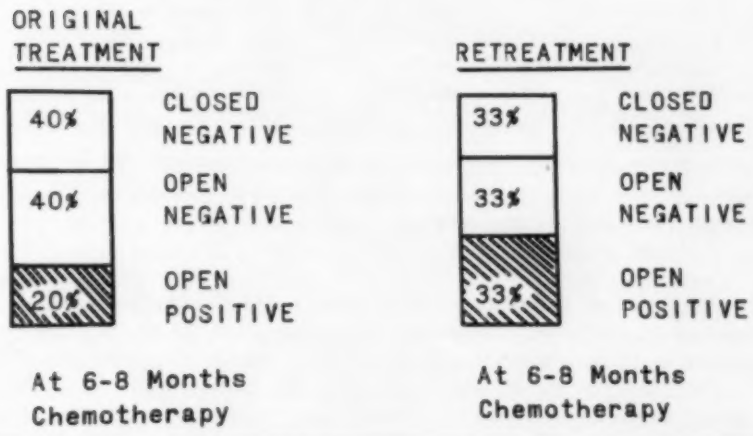
Preliminary results[8] in comparing patients with and without cavity apparent at the onset of treatment suggest that filled-in or inspissated cavities with blocked broncho-cavitary junction are more uncertain in prognosis than necrotic lesions which have never sloughed. Whether such a clinical distinction will be substantiated remains to be determined.

Open Negative Group

While the majority of patients (80 per cent) will have sputum negative for tuberculosis at six to eight months, at least half will still have residual open lesions (Table III). This group demonstrating residual annular shadows are perhaps more important than those with closed lesions. The long association of cavity as a portent of relapse in tuberculosis has made the prognosis uncertain in these patients. There are many reasons to be-

TABLE III

INCIDENCE OF OPEN NEGATIVE PATIENTS



lieve that the combination of negative sputum and cavitary lesions is a phenomenon peculiar to effective chemotherapy. No such incidence of so-called "open negatives" was seen in the predrug era.

Without entering into a discussion of the pathogenesis of open lesions or the concept of open healing, we shall attempt to define our criteria for surgery and indicate the results in resected and non-resected groups.

Although the words open and cavity have heretofore been used synonymously it is well to recall that all open lesions are not *a priori* cavities. While the majority (62 per cent in our material) of these annular shadows were characteristic tuberculous cavities, other pathology such as dilated or cystic bronchi or areas of focal hypertrophic ephysema was found as radiographic facsimiles of cavity.

Because of uncertainty in defining which radiolucent areas were dangerous cavities and which would yield viable bacilli; in addition to a relapse rate of nearly 50 per cent in our early experience with 43 open negative patients,[9] a systematic attempt has been made since 1951 to treat all open negative patients, who were satisfactory surgical candidates, by pulmonary resection.

Medical Series

From a group of 536 consecutive patients starting original chemotherapy prior to Dec. 31, 1954, 118 were open negative when evaluated after six to eight months of therapy. Each patient had x-ray film evidence of cavity and sputum positive for tuberculosis at the onset of treatment.

Following six to eight months of antituberculous drugs, these patients were observed to have had negative sputum for three consecutive months or longer, yet disclosed persistent annular shadows by careful planography.

TABLE IV
TUBERCULOUS RELAPSE 118 MEDICALLY TREATED
OPEN NEGATIVE PATIENTS

Relapse	No. of Cases	Interval After Observation Point	
Bacteriologic	16	Within one year	37
Radiologic	15	Bacteriologic	17
Combined (X-ray & Bacty.)	20	X-Ray	11
		Combined	9
TOTAL	51(43%)		

Although potential surgical candidates, these 118 patients did not receive surgical treatment for one or more reasons.

Results

In this group of 118 open negative cases a radiologic relapse which was defined as any unfavorable change, occurring after the observation point, was seen in 15 patients without concomitant bacteriologic relapse (Table IV). Bacteriologic relapse which was defined as evidence of tubercle bacilli, by either smear or culture, was found in 16 patients, not associated with simultaneous x-ray film activity. The more common pattern of relapse, however, was manifested by a combination of radiologic change and the demonstration of positive bacteriology occurring in 20 patients. In many instances, so-called bacteriologic escape was the first unfavorable change to be noted. The presence of bacterial resistance to one or more drugs was often apparent at this time.

A total of 51 (43 per cent) have relapsed in a follow-up period extending through three post treatment years: 29 while chemotherapy was still being given; 22 after it had been stopped. Most of the relapses occurred early: 37 within one year and 46 within two years of the Observation Point.

Surgical Series

From January, 1951 to December, 1954, a total of 153 patients received 189 pulmonary resections on one or both lungs. This group satisfied the bacteriologic criteria of three consecutive negative monthly sputum cultures and a radiologic estimate of a persistent annular shadow at the time of surgery.

Because of the well known difficulties in precise interpretation of cavity presence, near the beginning of the study we arbitrarily adopted the terms equivocal and unequivocal to describe the estimated state of openness of the lesion. All planigrams within three months of operation were

TABLE V
OPEN NEGATIVE PATIENTS
EVIDENCE OF CAVITY BY PREOPERATIVE RADIOGRAPHY

Original Treatment	70 Patients	Retreatment	83 Patients
Equivocal Open Lesion	28	Equivocal Open Lesion	30
Unequivocal Open Lesion	42	Unequivocal Open Lesion	53

TABLE VI
SURGICALLY TREATED OPEN NEGATIVE PATIENTS

Type of Operation		Type of Operation	
Single or Multiple Wedges	27	Unilateral	117
Segments (one or more)	105	Bilateral	36
Lobectomy	53	All Palpable Disease	114
Pneumonectomy	4	Residual Disease	74
TOTAL	189		

reviewed and the annular shadows classified as equivocal or unequivocal (Table V).

The majority of tuberculous lesions in these patients have been discrete enough to allow segmental resection (Table VI). Those who demonstrated some degree of bacillary resistance to one or more drugs in cultures prior to conversion of the sputum state, were regarded as having uncertain drug control at the time of surgery. In these (approximately 10 per cent) lobectomy was the preferred type of resection.[10] Single or multiple wedge resections were utilized whenever feasible, but most often in those receiving original drug regimens. Multiple wedging of residual closed lesions was often supplementary to segmental or lobe resection, in an effort to establish a surgically treated group in whom all palpable disease had been removed.

Surgical Complications and Relapse

Both the immediate and late complications related to the operative procedure are given in Table VII. The majority of such morbidity occurs during the first two postoperative weeks and is non-tuberculous. In the sense that such complications represent mechanical problems incident to pulmonary resection, they are benign, easily treated and do not prolong the patient's ultimate discharge.

The major postresection complications have been seen in a small group of eight patients, each of whom had a sub-lobar type of resection in the left upper lobe (Table VIII). These medical and surgical failure consisted of tuberculous reactivation in the operative site or in the remaining segments of the upper lobe. Four of these patients were treated by secondary resection (lobectomy) of the involved area. The details of pathogenesis of implantation tuberculosis as learned from the gross and microscopic examination of primary and secondary specimens in eight patients with

TABLE VII
SURGICAL COMPLICATIONS 153 RESECTED OPEN NEGATIVE PATIENTS

Non-Tuberculous		Tuberculous	
Pneumothorax	30	Tuberculous Reactivation	4
Hemopneumothorax	5	Occult Bronchopleural Fistula and Tuberculous Reactivation	4
Bronchopleural Fistula	6		
Pneumonia	2		
Operative Accidents	2		

TABLE VIII
TUBERCULOUS RELAPSE 153 RESECTED OPEN NEGATIVE PATIENTS

Relapse		Interval Post-Op.
Operated Side (X-ray & Bacteriologic)	8	2 Weeks to 2½ Years
Non-Operated Side (X-ray Only)	2	2 Months & 6 Months
Undetermined (Bacteriologic Only)	3	1 Month to 6 Months
TOTAL	13	

occult postresection bronchial fistulas (four of whom were open negatives) are described in another report.[11]

Of the remaining four patients with postresection reactivations, each had received a segmental resection in the left upper lobe. All four exhibited new areas of infiltration in the remaining lingular segments. No cavity or infected operative site was demonstrated by appropriate studies, however, and for various reasons secondary resections were not performed.

In addition to these eight patients who demonstrated combined bacteriological and x-ray film relapse, five others had either single positive cultures in the postoperative period or unfavorable x-ray film changes. No change in treatment was instituted and subsequent follow-up over an 18 months period has shown no further relapse.

Gross Pathology and Bacteriology in Resected Specimens

The major findings in the resected specimens have been tabulated (Tables IX, X). In the entire group of 189 specimens, a total of 120 specimens (63 per cent) were found to have open lesions. On the other hand, such lesions were not disclosed in 69 specimens (36.5 per cent) even after careful recutting of the fixed material. Mayock and co-workers have demonstrated that many of these lucent areas are simulated by closed lesions containing centers of solid or liquid material.[12]

The presence of any amount of necrotic material was sufficient to consider 62 specimens as presenting dirty cavities. The majority of these

TABLE IX
MORPHOLOGY AND BACTERIOLOGY
189 OPEN NEGATIVE RESECTED SPECIMENS

	TOTAL	Open Lesions Positive	Open Lesions Negative Closed Lesions Positive	Total Specimens Positive
Open Lesions All	120	32	17	49 (41%)
Dirty Cavities	62	28	11	39 (62%)
Clean Cavities	58	4	6	10 (17%)
Closed Lesions	69			20 (28%)

TABLE X
OPEN NEGATIVE PATIENTS
CORRELATION RADIOLOGY, PATHOLOGY, BACTERIOLOGY

Pre-Op. X-Ray	Number of Cases	Number With Open Lesions	Positive Culture Open Or Closed Lesions
Unequivocal Cavity	95	79 (83%)	34 (36%)
Equivocal Cavity	58	29 (50%)	16 (55%)
TOTAL	153	108 (70.5%)	50 (33%)

lesions were characteristic parenchymal tuberculous cavities. However, 58 of the open lesions were recognized as clean cavities.

A correlation was made (Table X) of the preoperative impression of an equivocal and unequivocal open lesion with the demonstration of such finding in the resected material. Cavitary lesions were found in over three-quarters (83 per cent) of resected material from patients with uneqivocal annular shadows. However, the group with equivocal preoperative x-ray film evidence of open lesions disclosed a lower incidence of cavity (50 per cent) in the operative specimen. These data suggest that reasonably accurate interpretations can be given to the definition of annular shadows occurring during treatment.

Results of bacteriologic study are given in Table IX. The most important finding is the recovery by culture or guinea pig of viable tubercle bacilli in 38 per cent of the resected specimens. This figure represents the yield from any lesion in the specimen. In most instances, organisms were recovered from the open lesions (41 per cent). Occasionally, an adjacent unsloughed or filled in lesion might yield bacilli when the cavity was bacteriologically negative (14 per cent). In those specimens without evidence of an open lesion, organisms were recovered in 20 of 69 (28 per cent).

Follow-Up

Non-Resected Group

Follow-up of this group (118 cases) has been quite complete: of those at risk for relapse, one year follow-up was available on 96 per cent, two year follow-up on 92 per cent and three years on 86 per cent. The current status of the medical or non-resected group is presented in Table XI. Of

TABLE XI
CURRENT STATUS
118 MEDICALLY TREATED OPEN NEGATIVE PATIENTS

Inactive	90 (76%)	Active	15	(12%)
Never Relapsed	67	Deceased	13	
Relapsed	23	Tuberculous	8	
but inactive from—		Non-Tuberculous	5	
1. Continuing Treatment				
2. Retreatment Chemotherapy				
3. Surgery				

TABLE XII
153 SURGICALLY TREATED OPEN NEGATIVE PATIENTS

Inactive	133	(87%)	Deceased (Non-Tbc.)	4
Active	6	(4%)	Lost to Follow-Up	10

the 90 patients (76 per cent) now considered to be inactive, 67 never demonstrated relapse. The remaining 23 relapsed at varying intervals from the Observation Point (six to eight months) but were converted to an inactive status by 1) continuing original drugs, 2) retreatment or new drug combinations, 3) later pulmonary resection.

Fifteen (12 per cent) of the original group are still considered active and most are in the hospital. There were eight deaths from tuberculosis and five from non-tuberculous causes.

Resected Group

Each patient in the surgical group received a minimum of six months postoperative chemotherapy. In the event viable tubercle bacilli were recovered from the resected material and residual disease remained in the operated lung, the period of postresection treatment was extended to nine or 12 months.

The current status of the resected group is given in Table XII. The last patient included in this review was operated in December, 1954. Thus, a minimum of one year, and for the majority, a two and three year record of follow-up data is available. Ten were lost to the study in spite of repeated efforts at contact. There was no postoperative death, the four deaths in the series being of non-tuberculous causes. A total of 133 (87 per cent) of the original 153 patients, are classified as inactive. Four are receiving retreatment chemotherapy. The site of activity is believed to be in the operated lung.

Discussion

Because there are no reliable x-ray criteria for determination of the anatomic age of closed lesions, the accurate selection of resection candidates is difficult. It has been shown that healing may not proceed in a uniform manner from one patient to the next though both have similar lesions for similar treatment periods. Indeed necrotic residual disease may behave unpredictably in two adjacent lesions of the same lobe.[13]

At present there are no clinical, pathological or bacteriological data which permit the routine resection of non-cavitary lesions. Indications for resection remain confined to a small group (perhaps 5 to 10 per cent) in whom clinical experience suggests relapse is probable or in those who after sufficient observation have demonstrated instability of the residual focus.

Similarly the problem of recommending surgery for the non-infectious patient with an open lesion results from our inability to select the dangerous lesion. Any such assumption is at best an estimate based on the predicted pathology of the lesion in question and careful evaluation of the clinical background in an individual case. Rather than recommend sur-

gery for patients with closed or open lesions in whom it may be unnecessary two alternative plans of treatment are presented:

1. Allow closed or open lesions to demonstrate unfavorable change or bacteriological relapse before advising resection.
2. Anticipate relapse in certain clinical situations. Included in this category are:
   a) Unequivocal open lesions.
   b) Resistant organisms prior to sputum conversion.
   c) X-ray film or bacteriologic change during treatment.

SUMMARY

Indications for resection in the non-infectious patient with a closed lesion have been presented. The results of non-resection in 136 patients with a relapse incidence of 14 per cent are contrasted to that of 9 per cent in 90 resected patients.

In the sputum negative patient with a residual open lesion a comparison of 118 non-resected with 153 resected patients gave a relapse incidence of 43 per cent for the medical series extending through three post-treatment years and 9 per cent for the surgical group. At present 90 of 118 medical patients (76 per cent) are considered inactive while 133 of 155 surgical patients (87 per cent) are inactive.

In the latter group (open negatives) the indications for surgery have included all patients who were satisfactory candidates. This policy has been supported by the relatively high relapse rate (43 per cent) of the non-resected patients and the recovery of viable tubercle bacilli in 38 per cent of the resected specimens.

The problem of selection may well resolve itself if pulmonary surgery is reserved for those patients whose lesions have demonstrated their instability during the treatment period or thereafter.

Acknowledgment: I am indebted to Dr. J. W. Raleigh, Chief, Tuberculosis Service, V. A. Hospital, Sunmount, New York, for data on the medical series in this report.

RESUMEN

Las indicaciones para resección en enfermos no infecciosos con una lesión cerrada, se presentan. Los resultados de la no-resección en 136 enfermos con una incidencia de recaídas de 14 por ciento está en contraste con el 9 por ciento ne los resecados.

En el erfermo con esputos negativos con una lesión residual abierta se hizo una comparación de los 118 no resecados con 153 resecados y se obtuvo una proporción de recaídas de 43 por ciento en la serie médica abarcando tres años después del tratamiento y 9 por ciento en 1 los resecados. Al presente, 90 de 118 enfermos tratados médicamente (76 por ciento) se consideran inactivos en tanto 113 de 155 quirúrgicos (87 por ciento) son inactivos.

En el último grupo (negativos abiertos) las indicaciones para la cirugía han incluído todos los enfermos que eran candidatos satisfactorios.

Esta actitud es respaldada por la proporción relativamente alta de recaí-

das (43 por ciento) de los no resecados y el haber encontrado bacilos viables en 38 por ciento de los especímenes de resección.

El problema de la selección puede resolverse por sí solo si la cirugía se reserva para los enfermos cuyas lesiones han demostrado la inestabilidad durante el período de tratamiento o después.

RESUME

L'auteur présente les indications de la résection chez les malades non bacillifères, atteints d'une lésion fermée. Chez 136 malades de ce type pour qui ne fut pas pratiquée de résection, le pourcentage de rechutes fut de 14% et contraste avec le pourcentage de 9% chez 90 malades qui subirent une résection.

Chez les malades à bacilloscopie négative, atteints d'une lésion résiduelle ouverte, une comparaison entre 118 malades qui ne subirent pas de résection et 153 opérés donna un pourcentage de rechute de 43% pour le groupe ayant subi un traitement médical, s'étendant à trois ans de contrôle après traitement, et 9% pour le groupe ayant subi un traitement chirurgical. Actuellement, 90 des 118 malades médicaux (76%) sont considérés comme stabilisés, tandis que 133 des 155 malades chirurgicaux (87%) sont stabilisés.

Dans le dernier groupe (lésions ouvertes, bacilloscopies négatives) les indications chirurgicales ont compris tous les malades qui étaient des candidats satisfaisants. Cette discipline a été renforcée par la constatation du taux de rechute relativement élevé (43%) chez les malades non-opérés, et la constatation de bacilles virulents dans 38% des pièces opératoires.

Le problème du choix peut résoudre aisément si l'on admet que la chirurgie pulmonaire est réservée à ceux des malades dont les lésions ont fait preuve d'instabilité pendant la période de traitement ou par la suite.

ZUSAMMENFASSUNG

Es wurden die Indikationen besprochen zur Resektion bei nicht ansteckungsfähigen Patienten mit geschlossen Herden. Die Ergebnisse bei nicht erfolgter Resektion an 136 Patienten mit einer Häufigkeit der Rückfälle von 14% werden gegenüber gestellt solchen von 9% bei 90 resizierten Kranken.

Hinsichtlich der im Sputum negativen Patienten mit einem restierenden den offenen Herd ergab einen Vergleich von 118 nicht resezierten mit 153 resezierten Patienten eine Häufigkeit der Rückfälle von 43% für die konservativ behandelte Gruppe, die sich über 3 Jahre nach der Behandlung erstreckte, und 9% für die chirurgisch behandelte Gruppe. Zur Zeit werden 90 der 118 konservativ behandelten Patienten (76%) als inaktiv angesehen, während 133 der 155 chirurgisch behandelten Pazienten (87%) inaktiv sind. In der zuletzt besprochenen Gruppe der offenen negativen Fälle umfasste die Indikation zum operativen Eingriff alle Patienten, die befriedigende Kandidaten waren. Diese Methode fand ihre Unterstützung in der relativ hohen Rückfallshäufigkeit von 43% unter den nicht resezierten Patienten und der Wiedergewinnung lebensfähiger Tuberkelbazillen

in 38% der resezierten Präparate. Das Problem der Selektion kann sich von selbst lösen, wenn die Lungenchirurgie solchen Patienten vorbehalten bleibt, deren Befunde ihre Instabilität während der Behandlungsperiode oder später bewiesen haben.

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The Role of Chlorpromazine in the Treatment of Bronchial Asthma and Chronic Pulmonary Emphysema*

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It is often difficult to achieve adequate sedation without concomitant respiratory depression in patients with bronchial asthma and chronic pulmonary emphysema. The deleterious and occasionally fatal effects of morphine in these disease states are well known.[1-4] This agent is a primary and continuous depressant of respiration even with doses too small to produce sleep or disturb consciousness.[5] These doses diminish the normal respiratory response to the inhalation of low concentrations of carbon dioxide. The harmful effect of morphine has been attributed in part to an increase in bronchomotor tone.[2,3] Herschfus et al[4] considered meperidine to be a useful and safe drug in the treatment of acute asthma or of status asthmaticus. Pulmonary function improved in most of their cases. However, these authors warned against the use of repeated and increasing doses which might result in respiratory depression. Rasor and Crecraft[6] stressed the frequency of meperidine addiction acquired in the treatment of bronchial asthma. Barbiturates in small doses as well as morphine have been demonstrated to depress the effective alveolar ventilation and produce respiratory acidosis in patients with chronic pulmonary emphysema.[7]

Recent reports relevant to the use of chlorpromazine (Thorazine) in bronchial asthma have been favorable.[8-11] It was therefore decided to investigate the role of this agent in the treatment of bronchial asthma and pulmonary emphysema.

Methods

Ten patients with uncomplicated bronchial asthma, six with bronchial asthma and chronic pulmonary emphysema, and 19 with primary chronic diffuse obstructive pulmonary emphysema, were studied clinically. Chlorpromazine was given as a single intramuscular dose of 25 to 50 mg. in some instances. In others it was administered orally or intramuscularly in similar quantities in combination with therapy designed to improve pulmonary ventilation and arterial blood gas content. These measures included IPPB (intermittent positive pressure breathing with a nebulized bronchodilator and detergent**) with oxygen, antibiotics, expectorants, aminophyllin, mechanical elimination of bronchial secretions and, in some instances, adrenocotical steroids and Diamox.

*From the Medical Service, Veterans Administration Hospital.

**Aerolone compound and zephiran hydrochloride (1:1000 aqueous).

The clinical status of each subject was evaluated by at least two observers. Patients whose respiratory distress was felt to be wholly or in part related to other entities than bronchial asthma or chronic pulmonary emphysema were excluded from this study.

Twenty-one patients with chronic diffuse obstructive pulmonary emphysema were also studied in the laboratory under basal conditions. Minute volume of respiration was collected in a Douglas Bag and measured in a dry gas meter.* Arterial blood was collected anaerobically with an indwelling needle. *p*H was determined with a Cambridge Model R *p*H meter. Arterial blood carbon dioxide and oxygen content and oxygen capacity were measured on the van Slyke apparatus.[12] Arterial blood carbon dioxide tension was estimated with a nomogram based on the Henderson-Hasselbach equation.[13] These measurements were performed immediately prior to and one hour after the intramuscular administration of 25 to 50 mg. chlorpromazine. Blood pressures were checked repeatedly with a sphygmomanometer.

Results

The effects of the drug in the 10 patients with uncomplicated bronchial asthma were as follows: Single 25 mg. intramuscular doses were followed by marked diminution of wheezing and restlessness within 15 to 30 minutes in five instances. One of these patients maintained a satisfactory course when the oral preparation was combined with a bronchodilator and expectorant for the following six days. No change occurred in two subjects within one hour after injection. Chlorpromazine was combined with other therapy in three cases. Drug-induced vomiting (aminophyllin) was alleviated in one and subsidence of wheezing with relaxation occurred in the other two patients.

Of the six patients with bronchial asthma and chronic pulmonary emphysema distinct lessening of dyspnea and wheezing was noted after a single intramuscular dose in one subject. Similar benefits occurred in two patients when the drug was combined with conventional bronchodilator therapy. Drug-induced emesis (aminophyllin) was alleviated in one instance. Drowsiness without amelioration of dyspnea ensued in one subject. No effect was achieved in one patient. These two severely ill patients did not respond to conventional measures. Adrenocorticotropic hormone was followed by remission in each.

Of the 19 patients with primary chronic diffuse obstructive pulmonary emphysema relief of marked respiratory embarrassment with wheezing and cyanosis was achieved in one instance when the agent was given as a single intramuscular dose. Aminophyllin-induced vomiting was controlled when it was administered orally to the same subject over a period of eight days. Eight patients exhibited a favorable hospital course, with relaxation and control of restlessness and irritability on "combined" therapy. An additional subject received four different courses of Thorazine, in combination with intensive therapy, for a total of 164 days. Adequate relaxation

*American Meter Company, Albany, N. Y.

TABLE I

Case	Dose (mg.)	Minute Volume (L/min./M²) Before	Minute Volume (L/min./M²) After	$PaCO_2$ (mm. Hg.) Before	$PaCO_2$ (mm. Hg.) After	Arterial O_2 Saturation % Before	Arterial O_2 Saturation % After	Arterial pH Before	Arterial pH After	Blood Pressure (mm. Hg.) Before	Blood Pressure (mm. Hg.) After	Remarks
1	25	3.8	4.9	40	37	79.6	88.1	7.44	7.50	112/70	92/60	Dry mouth; drowsy
2	25	5.7	6.3	43	42	88.1	85.1	7.35	7.36	110/80	90/60	Asleep
3	25	5.6	5.9	38	41	92.5	90.3	7.43	7.41	160/80	140/90	Asleep
4	25	5.0	3.8	48	53	92.0	82.0	7.36	7.35	104/60	94/60	Drowsy
5	25	4.6	7.9	55	56	94.9	94.4	7.35	7.33	130/80	130/70	No change
6	25	5.6	6.9	58	60	76.5	74.5	7.41	7.41	110/66	120/60	Asleep
7	25	4.5	3.9	38	38	*		7.48	7.51	120/80	120/80	Drowsy
8	25	4.4	4.4	37	37	93.1	86.3	7.48	7.51	120/70	100/65	No change; relaxed
9	25	6.6	6.1	34	38	*		7.51	7.48	130/80	130/80	Asleep
10	25	6.2	5.6	43	45	95.0	89.3	7.40	7.41	130/70	110/60	Asleep
11	50	4.0	3.9	36	35	97.0	96.4	7.48	7.49	.....	.....	Drowsy
12	50	5.5	4.4	42	40	93.2	88.1	7.45	7.47	120/68	125/70	Asleep
13	50	6.3	4.0	53	51	88.6	85.0	7.42	7.44	100/70	100/60	Asleep
14	25	**		59	64	56.9	50.4	7.42	7.38	110/64	100/60	Increased dyspnea; semistuporous
15	25	*		24	25	87.9	90.6	7.56	7.55	104/70	112/70	No change
16	25	***		50	51	63.8	63.3	7.47	7.46	116/70	130/60	Became relaxed
17	25	3.5	2.9	41	41	80.7	79.0	7.43	7.43	120/80	114/72	Relaxed; no change
18	25	5.7	6.0	42	42	82.5	86.0	7.50	7.50	130/80	134/80	Relaxed
19	50	5.2	5.4	31	31	91.2	95.3	7.49	7.48	102/70	112/80	Asleep
20	50	4.7	4.3	46	47	83.5	87.5	7.40	7.41	100/50	100/80	Relaxed
21	25	5.8	5.9	52	54	81.2	73.7	7.46	7.46	105/80	88/60	Decreased dyspnea
Mean		5.2	5.1	43	44	85.2	83.4	7.44	7.45			
SD md		±1.18		±2.18		±4.74		±0.02				

*Technical difficulty
**Too drowsy to cooperate
***Patient uncooperative

md—mean difference

and control of the mental symptoms of carbon dioxide intoxication were achieved during three of these courses. Temporary clinical improvement with sedation occurred during the fourth course, before the eventual fatal outcome.

Despite adequate relaxation, clinical improvement was not attained by intensive therapy in nine subjects. Five of these died after receiving chlorpromazine from three to 33 days. In view of the severity of the disease in this group, it is difficult to ascribe any untoward effect of the drug.

Wherever practicable, the head-low position was employed with the intramuscular administration of Thorazine. An additional patient sat up after 15 mg. were injected and was noted to be pulseless and cyanotic 30 minutes later. This subject was desperately ill, with pyloric obstruction and electrolyte disturbance, complicating his disease, and eventually succumbed.

There was no instance of jaundice or leukopenia in this series of 35 patients.

Table I is the summation of the physiologic measurements obtained before and one hour after administration of 25-50 mg. chlorpromazine intramuscularly. Drowsiness or sleep occurred in 19 of the 21 emphysematous subjects. There was no significant change in the mean values for minute volume of respiration, and the arterial oxygen saturation carbon dioxide tension (Pa_{co2}), and *p*H. The clinical status of one patient became alarming within one hour after drug administration. There was increased respiratory embarrassment and a state of semi-stupor. This patient responded to IPPB with oxygen therapy. It is emphasized that the clinical status of this individual was precarious prior to study, with marked hypoxia and hypercapnia. Only two subjects exhibited falls in diastolic pressure over 20 mm. Hg. The head-low position was maintained whenever possible.

Discussion

The pharmacologic properties of chlorpromazine have been reported by others.[14, 15] This agent depresses central and autonomic nervous systems. There is an anti-emetic effect. It is also anticholinergic, adrenolytic, antihistaminic, and antispasmodic. It has been claimed that the drug produces little or no respiratory depression,[10, 14, 15] although Dobkin et al reported decreased tidal volume with some increase in the oxygen consumption in 14 patients.[16]

Some authors[8, 11] have reported relief of bronchospasm in severe asthmatic crises with Thorazine. The experiences reported in this paper indicate that the drug is safe and effective when used singly or combined with conventional bronchodilator therapy in uncomplicated bronchial asthma and in some cases complicated by pulmonary emphysema.

When the irreversible changes of chronic diffuse obstructive pulmonary emphysema are present, this effect is less apt to occur. In this group, chlorpromazine was employed primarily for its relaxant qualities. As stated in the introduction, the problem of adequate and safe sedation in this disease is often vexing.

Any agent which induces relaxation quickly with little respiratory depression should facilitate the administration of intensive therapy, including the various mechanical measures employed in the treatment of severe pulmonary emphysema.

From the evaluation of the emphysematous subjects on chlorpromazine combined with intensive therapy described previously, it may be concluded that chlorpromazine appears to satisfy this requirement. The physiologic data obtained incident to single intramuscular dose administration offer no evidence for respiratory depression in the 21 patients studied.

SUMMARY

Clinical experiences with the use of Thorazine in 35 patients with bronchial asthma and/or chronic pulmonary emphysema are reported. The effect on minute volume of respiration and arterial blood gases and *p*H, was determined in 21 patients with chronic diffuse obstructive pulmonary emphysema.

It is concluded that the drug may be safely and effectively administered, either singly or in combination with known bronchodilator agents, in the therapy of paroxysms of bronchial asthma. In chronic pulmonary emphysema, chlorpromazine appears to be a useful adjunct, in combination with intensive therapy designed to correct pulmonary ventilation.

RESUMEN

La experiencia clínica en el uso de la Toracina en 35 enfermos de asma y/o enfisema pulmonar crónico se relatan.

Los efectos sobre el volumen minuto de la respiración y los gases arteriales y pH, fué determinado en 21 enfermos con enfisema crónico obstructivo.

Se concluye que la droga puede ser administrada con seguridad y eficacia ya sea sola o en combinación con los agentes broncodilatadores en el tratamiento del paroxismo de asma. En el enfisema crónico pulmonar la cloropromazina parece ser un adyuvante útil en combinación con la terapia adecuada para corregir la ventilación pulmonar.

RESUME

Les auteurs rapportent leur expérience clinque de la "Thorazine" chez 35 malades, atteints d'asthme bronchique associé ou non à l'emphysème pulmonaire chronique. L'effet sur le volume respiratoire minute, sur les gaz du sang artériel et le pH, fut déterminé chez 21 malades atteints d'emphysème pulmonaire obstructif chronique et étendu.

Les auteurs arrivent à la conclusion que la médication peut être administrée efficacement et sans danger, soit seule, soit en association avec des agents bronchodilatateurs connus, dans le traitement des atteintes aiguës d'asthme bronchique. Dans l'emphysème pulmonaire chronique, la chlorpromazine semble être un appoint utile, en association avec un traitement énergique destiné à améliorer la ventilation pulmonaire.

ZUSAMMENFASSUNG

Bericht über klinische Erfahrungen beim Gebrauch von Thorazin bei 35 Patienten mit Bronchial-Asthma und/oder chronischem Lungenemphysem. Es wurde die Wirkung auf das Atem-Minuten-Volumen und die arteriellen Blutgase sowie pH bestimmt bei 21 Kranken mit chronischem diffusen obstruktivem Lungenemphysem.

Es wird der Schluss gezogen, dass das Mittel mit Sicherheit und guter Wirksamkeit angewandt werden kann, sei es allein, oder in Verbindung mit bekannten bronchodilotatorischen Stoffen zur Teraphie von Anfällen von Bronchial-Athma. Beim chronischen Lungenemphysem dürfte das Chlorpromazin ein nützliches Hilfsmittel sein in Kombination mit einer intensiven auf Besserung der pulmonalen Ventilation gerichteten Therapie.

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Case Report Section

Mediastinal Lipoma

J. F. ALDEN, M.D., F.C.C.P., R. B. G. BJORNSON, M.D., E. R. STERNER, M.D. and J. L. SPRAFKA, M.D., F.C.C.P.

St. Paul, Minnesota

Lipomas, though common tumors elsewhere, have rarely been found in the mediastinum and actually have received little consideration in the differential diagnosis of intrathoracic tumors. An excellent and comprehensive review by Keeley and Vana[1] states that only 46 cases of lipomas located entirely intrathoracically have been reported and that the number of patients surviving the removal of such tumors is only 35. They were careful to differentiate between the lipothymomas with lymphoid tissue and Hassal's corpuscles and the rarer true lipomas composed entirely of adult fat.

Case Report—A 49 year old plumber of Scandinavian descent, complained of an annoying cough of five years duration which had grown worse over the past two years. He had noticed slight dyspnea, particularly when stooping over. He had no other pertinent symptoms or abnormal physical findings.

He had consulted several physicians about his cough and 14 months prior to admission a chest roentgenogram made elsewhere revealed an upper mediastinal mass, which was thought to be an aneurysm. From another physician he received desensitization therapy for an allergic condition, with subjective improvement of the cough.

A submucous resection was done for deviated septum which interfered with nasal ventilation. During this same hospital admission, fluoroscopic and roentgenographic examination of the chest was made (Figure 1) because of the past history. The mass appeared to have enlarged by about 30 per cent. The lateral view (Figure 2) showed displacement of the trachea anteriorly by the mass. Fluoroscopically intrinsic pulsa-

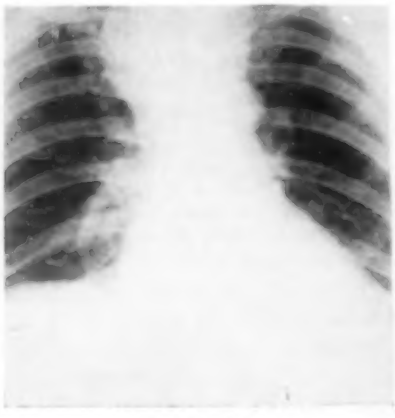

FIGURE 1A

FIGURE 1B

Figure 1A shows tumor outlined in antero-posterior projection.—In *Figure 1B* notice anterior displacement of trachea in lateral projection.

From the Departments of Surgery and Radiology, Bethesda Hospital.

tions could not be detected, but transmitted pulsations from the aorta were observed. Valsalva and Mueller maneuvers caused no apparent change in the size of the mass.

With the patient in the lateral position, the fourth right rib was resected and the tumor easily located and dissected from the mediastinum. It was dumb-bell in shape, and measured 8 x 12 x 5 cm. in size. Its greatest bulk lay in the right chest and it crossed the mediastinum to impinge on the lesser curvature of the aortic arch. The mass was superior to the azygos vein and displaced the trachea anteriorly and the esophagus slightly to the right. The superior vena cava lay posteriorly. Grossly and by histopathological examination, the tumor was a lipoma.

Following surgery he made an uneventful recovery and has been free from symptoms. He has no other detectable lipoma.

DISCUSSION

The enlargement of the mediastinal mass as seen by x-ray examination, suggested a malignant lesion. It is felt that, if such lesions are reported, perhaps they will enter more prominently into the differential diagnosis of thoracic tumors. This is of value because the malignant and discouraging nature of many mediastinal and intrathoracic tumors sometimes influences the physician against surgery.

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Scalenus Anticus Syndrome — A Late Sequela of Thoracoplasty*

TAKESHI OKANO, M.D.

Oteen, North Carolina

Thoracoplasty is still a common procedure in the treatment of pulmonary tuberculosis and empyema spaces of non-tuberculous and tuberculous diseases. With the present physical therapeutic regime, significant complications of the musculoskeletal system are few. Chest deformity, kyphoscoliosis, chest pain and shoulder and scapula difficulties are the more common complaints.

An intensive search in the American and foreign literature has not revealed reports of cases of scalenus anticus syndrome as a late sequela of thoracoplasty. It is supposed that such cases have been overlooked and that the symptoms of neck, shoulder and arm pain have been delegated to non-treatable musculoskeletal deformities. It is the purpose of this paper to urge closer scrutiny of patients with post-thoracoplasty pain such that this easily treatable condition may not be overlooked.

The causes of scalenus anticus syndrome are varied although often unknown. In thoracoplasty, as the scalenus anticus muscle is stripped off the scalene tubercle, it becomes non-functioning; thence it undergoes atrophy of disuse in association with decreased vascularity: the final result being a taut fibromuscular band compressing the brachial plexus or their roots.

*From the Veterans Administration Hospital.

Another mode of causation of the syndrome, although highly speculative, is by elongation of the distance between the insertions and origins of the anticus and medius, thus compressing the brachial plexus. This can be obtained if the muscles remain attached to the periosteum which regenerates bone or by fixation in scar tissue at a more caudal position and secondly, by scoliosis with convexity of the cervical spine to the side of the thoracoplasty and rotation backward of the vertebrae, thus throwing the transverse processes posteriorly.

The following patients were observed at Veterans Administration Hospital, Oteen, North Carolina.

Case 1: A 32-year-old white man was admitted to this hospital in February, 1954 for treatment of active pulmonary tuberculosis. Diagnosis of tuberculosis was established in 1943, left thoracoplasty was performed in 1948 and right segmental resection in 1951. He complained of pain along the radial aspect of the arm, shoulder, numbness of the thumb and index finger on the left of about two years duration. Adson's test was negative. X-ray film did not reveal cervical rib but moderate thoracoplasty deformity (Figure 1).

Left scalenotomy was performed on July 23, 1954. The scalenus anticus muscle was found to be a narrow, avascular, fibrous, taut band closely applied in the groove be-

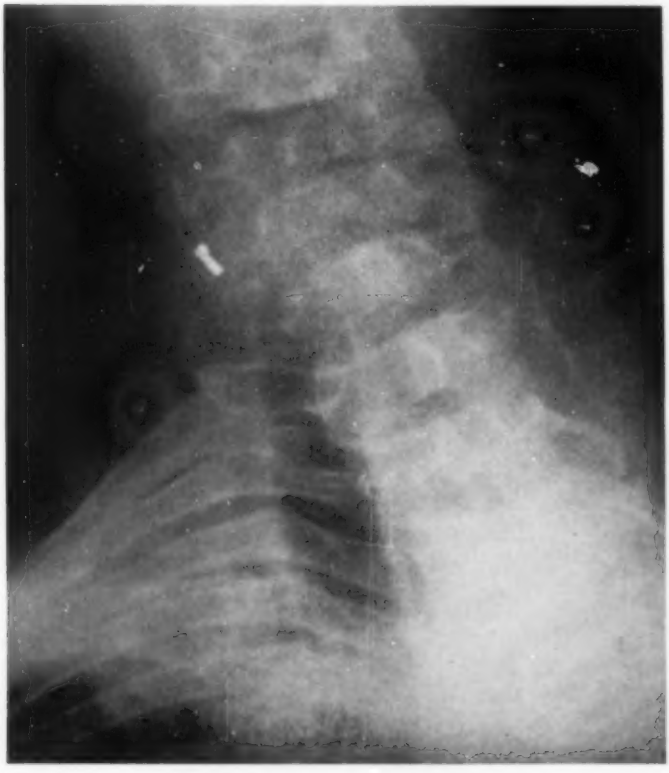


FIGURE 1 (Case No. 1): Pre-scalenotomy x-ray shows no cervical rib but moderate deformity of the spine.

tween the vertebral bodies and transverse processes. The insertion extended into the thoracic inlet and was not exposed. After section, the cut ends separated for about four centimeters.

Postoperatively, he was found to have complete relief from pain but numbness of the thumb had persisted to the last follow-up in September 1956.

The case illustrates the superior type of the syndrome in which the upper roots of the plexus (C 4, 5, 6) were compressed by the degenerated muscle. Relief was obtained except for involvement of portion of the sixth cervical root. It is felt that the findings at operation and relief obtained from scalenotomy indicate, although the symptoms appeared four years after thoracoplasty, that thoracoplasty was the causative factor of the syndrome. Earlier scalenotomy may have given him complete relief.

Case 2: A 46-year-old white man was admitted to this hospital in April 1954 with severe pain in the neck, shoulder, ulnar aspect of the arm and third, fourth and fifth fingers on the right of about eight months duration. He had right thoracoplasty performed in 1947 for cavitary pulmonary tuberculosis. Adson's sign was positive with definite obliteration of the radial pulse and accentuation of pain. X-ray film showed the usual thoracoplasty deformity (Figure 2), and no cervical rib. Right scalenotomy was performed in April 1954. The scalenus anticus muscle was found to be a fibrous, avascular, taut band which separated for a distance of about four centimeters after section. The last follow-up in May 1956 revealed complete relief of symptoms.

This patient illustrates the involvement of almost all of the nerve roots but principally of the lower. Symptoms appeared six years after thoracoplasty and relief was complete after scalenotomy.

These patients illustrate the long latent period before classical signs of scalenus anticus syndrome appeared and secondly, the long period of unnecessary discomfort before definitive therapy was carried out. The thoracoplasty patient in pain merits a thoughtful examination for this condition which can be easily treated.

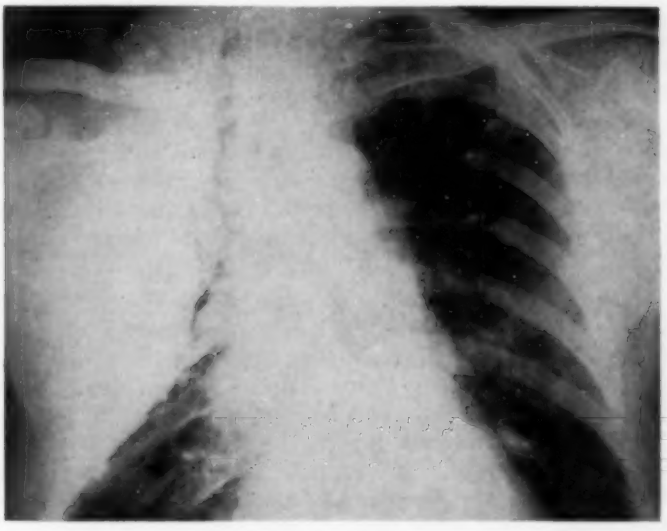


FIGURE 2 (Case No. 2): There is no cervical rib; however, there is slight amount of scoliosis and a good upper pulmonary collapse from the thoracoplasty.

Editorial

The Doctors' Crusade for Peace

The idea of compiling opinions on the benefits to be derived from medical interchange, either through international congresses or conventions as a means of "dissemination of knowledge and promotion of good will throughout the medical profession" and as a "factor in the ultimate establishment of world peace," is a most worthy one. Dr. Arnold S. Anderson expressed this concept in his splendid Editorial entitled "Doctors and Peace" (June 1955) when he referred to the long record of idealism of the medical profession which might well be taken as a real crusade in this sense.

The "Doctors' Crusade for Peace" seems quite logical. The histories of all countries are filled with old and new examples of doctors' efforts toward this goal, not only in their specific fields of endeavor but, likewise, in that of human relations for the peaceful improvement of mankind. For example, it is related that Dr. José Maria Vargas, the founder of medical studies in Venezuela, and president of the Republic in 1835, desired to raise to a dogma the fulfillment of the Law and the stabilization of civil authority. He found himself alone, assaulted by a mutinous mob clamoring for his resignation or the alternative of death, and answered the leader's "the world belongs to the valiant," with his famous, simple and solemn reply "the world belongs to the just," and thereby successfully resisted the absurd attempt.

In 1948, at a Venezuelan University in the Andes, a doctor was again the leader of a long campaign toward the establishment of The Faculty of Forestry to combat the erosion of the land, and floods with their cortege of hunger, misery, disease and death. Dr. A. J. Uzcátegui who, though neither statesman nor agronomist, knew how to evaluate, better than those more technically prepared, the biological complex known as "renewable natural resources," and now under the auspices of the F.A.O. the University has its forestry training center for all Latin American countries. It is an ambitious lesson of prophylaxis which treats the elimination of the first cause of disease.

Also in 1948, visiting with Dr. Jay Arthur Myers in Minneapolis, I received one of my greatest public health impressions: The dramatic story of the war against tuberculosis in Minnesota. On that occasion I visited the Live Stock Sanitary Board and Veterinarians of Minnesota. There I was shown the exemplary form of eradication of bovine tuberculosis in the State. This visit gave birth to the idea of implanting this tuberculosis bovine campaign in Venezuela which is being carried on very successfully; "Invited and Conquered" is a great truth which we doctors often experience.

The idea of international meetings to discuss not the destruction of mankind but the salvation of human life and its moral welfare, follows

the Bolivarian ideal. When our Liberator, Simón Bolivar, planned his Congress of Panamá, held in 1826, which was the first Assembly of Nations to discuss the peaceful future of mankind on a plan of equality and conviviality, his expression was "The Congress of Panamá shall unite all representatives of America. None shall be deemed weaker than another; none shall be stronger . . . The difference of origin and color shall lose its influence and power . . . Social Reform shall at last be achieved under the auspices of Liberty and Peace . . . Mankind shall give manifold blessings to this League of Health."

Our profession has prepared us to follow this path.

JOSÉ IGNACIO BALDÓ, M.D., F.C.C.P.*

*Chairman, Council on Pan-American Affairs, Caracas, Venezuela.

FINAL NOTICE
1958 DIRECTORY LISTINGS

If you have not returned the proof for your listing in the 1958 Directory of the College, please do so at once. Members may purchase copies of the 1958 College Directory by ordering immediately at the pre-publication price of $5.00. After publication the price will be $7.50.

The President's Page

The importance of an organization increases in direct ratio to the interest and cooperation evidenced by its membership. The large number of candidates, whose applications are now being reviewed by the Board of Regents, is a major proof of the constant interest of our members. Each of the applicants listed in the Roster of Candidates recently sent to every member of the College in the United States and Canada, has been proposed by a member of the College in good standing or by one of our state membership committees. This roster is not mailed to members in countries other than the United States or Canada since applicants in those areas are screened by the respective Governor and Regent prior to the publication of the Roster. Members, upon receipt of the Roster of Candidates, are requested to comment, favorably or unfavorably, upon applicants. The large number of letters received from the membership is gratifying to the Board of Regents and the information supplied by members is extremely helpful in the evaluation of an applicant's qualifications. Thus, each of our members shares in the responsibility of screening candidates and through his cooperation assists the Board of Regents in maintaining standards of membership.

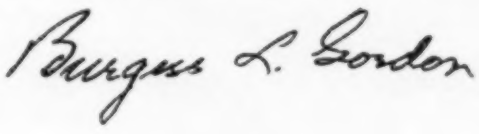
It is well, I believe, to emphasize the fact that the mere publication of an applicant's name does, in no way, indicate that his application will be approved or that he will be accepted for the type of membership for which he has applied. To insure careful and unbiased evaluation, all applications are presented to the Governor for the state or province in which the applicant practices. After the Governor has made his recommendations, the applications are reviewed by the Regent for the area and, finally, all applications are reviewed by the Chairman of the Board of Regents. Controversial cases are referred to the Executive Council for action after a full investigation has been made.

Of the 105 candidates for direct Fellowship or advancement to Fellowship whose applications have been filed between March 1 and September 1, 1957, over eighty-five per cent hold certification by one of the American Boards or the Royal College of Physicians and Surgeons. The balance of these applicants will be classified as Associate Fellows until they have successfully completed the oral and written examinations given by the College. Fellowship examinations are also given in several of the countries outside the United States and Canada and, upon the recommendation of College officials, physicians who are citizens of other countries and who are temporarily in the United States are examined during our annual or interim meetings.

Our method of processing applications offers every member of the College an opportunity to have a voice in membership activities and I want to thank all of you who have expressed an interest in the present group of applicants.

The Board of Regents, at the 23rd Annual Meeting of the College held in New York City, authorized the publication of the tenth edition of the college Directory. More than 1,100 new members will be listed in the 1958 Directory. Recently you were sent a proof of your listing and it is hoped that you have returned it to the Executive Offices in Chicago to assure publication of the correct information.

The splendid program to be presented at the Interim Session of the College in Philadelphia, December 2, 1957, is published in this issue of the journal. Please note that an advance registration and reservation form is included which we urge you to forward to the Executive Offices at once in order that you may be registered in advance and a place reserved for you at the discussion of your choice. I am looking forward to the pleasure of seeing many of our members at the meeting.



INTERIM SESSION PROGRAM

The Warwick Hotel, Philadelphia will be headquarters for the Interim Session of the College, December 2-3 and the Clinical Meeting of the American Medical Association will be held at the Civic Auditorium, Philadelphia, December 3 through 6. For hotel reservations please write direct to the Warwick Hotel, 17th and Locust Streets, Philadelphia 3; be sure to indicate that you will attend the meeting of the American College of Chest Physicians and give arrival and departure dates.

Dr. Robert V. Cohen, Philadelphia, Chairman of the Scientific Program Committee, has announced that the following program has been arranged by his committee, which is sponsored by the Pennsylvania Chapter of the College. On page xxv you will find an ADVANCE REGISTRATION AND RESERVATION FORM. Members planning to attend the meeting are urged to complete this form at once and sent it to the Executive Offices of the College in Chicago. Your badge, program, luncheon and dinner tickets will be awaiting your arrival at the College Registration Desk in the Walnut Room, 19th floor, Warwick Hotel.

MONDAY, DECEMBER 2

8:00 a.m.—REGISTRATION—Walnut Room, 19th Floor

8:55 a.m.—SCIENTIFIC SESSION—Washington Room

Co-Chairmen: **Robert V. Cohen**, Philadelphia, Pennsylvania
Donald R. McKay, Buffalo, New York

9:00 a.m.—*Respiratory Problems in the Neonatal Period*
Roy F. Goddard, Director, Pediatric Research Department, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico

9:15 a.m.—*Discussor:* **Arthur DeBoer**, Associate Attending Surgeon, Children's Memorial Hospital, Chicago, Illinois

9:20 a.m.—*Discussion from the floor*

9:25 a.m.—*Present Advances in Vascular Surgery*
Michael E. DeBakey, Professor of Surgery, Baylor University College of Medicine, Houston, Texas

9:40 a.m.—*Discussor:* **Osler A. Abbott**, Associate Professor of Surgery and Director, Division of Thoracic Surgery, Emory University School of Medicine, Emory University, Georgia

9:45 a.m.—*Discussion from the floor*

9:50 a.m.—*The Usefulness of Biopsy Techniques in Pulmonary Disease*
Laurence K. Groves, Senior Instructor of Thoracic Surgery, Frank E. Bunts Institute; Staff, Department of Thoracic Surgery, Cleveland, Ohio

10:05 a.m.—*Discussor:* **Karl P. Klassen**, Professor of Surgery and Chief, Thoracic Surgery Service, Ohio State University College of Medicine, Columbus, Ohio

10:10 a.m.—*Discussion from the floor*

10:15 a.m.—*Modern Concepts in the Dietary Treatment of Coronary Heart Disease*
Jeremiah Stamler, Assistant Director, Cardiovascular Department, Michael Reese Hospital; Established Investigator, American Heart Association, Chicago, Illinois

10:30 a.m.—*Discussor:* **Abraham Jezer**, Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City

10:35 a.m.—*Discussion from the floor*

10:40 a.m.—*Intermission*

10:55 a.m.—*Physical Methods of Enhancing the Efficiency of Ventilation in Pulmonary Emphysema*
Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City

11:10 a.m.—*Discussor:* **Albert H. Andrews, Jr.**, Associate Clinical Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois

11:15 a.m.—*Discussion from the floor*

11:20 a.m.—PANEL DISCUSSION

"The Management of Pulmonary Emphysema"

Moderator: **R. Drew Miller**, Instructor in Medicine, University of Minnesota Graduate Medical School, Rochester, Minnesota

Panel: **Hylan A. Bickerman**, Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City

Otto C. Brantigan, Professor of Clinical Surgery, and Professor of Clinical Anatomy, University of Maryland School of Medicine, Baltimore, Maryland

Harold A. Lyons, Associate Professor of Medicine, State University of New York College of Medicine, Brooklyn, New York

12:15 p.m.—ROUND TABLE LUNCHEONS

1) **PRESENT AND FUTURE DEVELOPMENTS IN HEART SURGERY**

Egbert H. Fell, Clinical Professor of Surgery, University of Illinois College of Medicine; Attending Surgeon, Presbyterian and Cook County Hospitals, Chicago, Illinois

Alfred Goldman, Chief of Thoracic and Cardiac Surgery, City of Hope Medical Center, Duarte; Associate Attending, Thoracic Surgery, Cedars of Lebanon Hospital, Los Angeles, California

Dwight E. Harken, Associate Clinical Professor of Surgery, Harvard Medical School; Surgeon, Peter Bent Brigham Hospital, Boston, Massachusetts

Moderator: **John F. Briggs**, Associate Professor of Clinical Medicine, University of Minnesota Medical School, Minneapolis, Minnesota

2) **LONG TERM RESULTS OF CHEMOTHERAPY IN TUBERCULOSIS**

Sumner S. Cohen, Assistant Medical Director, Glen Lake Sanatorium, Oak Terrace, Minnesota

Alfred S. Dooneief, Attending Physician, Montefiore Hospital, New York City

Robert A. Goodwin, Jr., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine; Chief, Tuberculosis Service, Thayer Veterans Administration Hospital, Nashville, Tennessee

Moderator: **William B. Tucker**, Director, Tuberculosis Service, Veterans Administration Central Office, Washington, D. C.

3) **ANTICOAGULANT THERAPY IN ACUTE AND CHRONIC CORONARY HEART DISEASE**

Henry I. Russek, Consultant in Cardiovascular Research, U. S. P. H. S. Hospital, Staten Island; Consultant, Cardiovascular Disease, Rockaway Beach Hospital, Rockaway, New York

Joseph M. Ryan, Associate Professor of Clinical Medicine, University of Minnesota Medical School

Sidney Sherlis, Assistant Professor of Medicine, University of Maryland School of Medicine; Attending Physician, University Hospital, Baltimore, Maryland

Moderator: **Simon Dack**, Assistant Clinical Professor of Medicine, New York Medical College; Chief, Pre-natal Cardiac Clinic, The Mount Sinai Hospital, New York City

4) **INHALATION THERAPY**

Gustav J. Beck, Instructor in Medicine, Columbia University College of Physicians and Surgeons, New York City

Maurice S. Segal, Clinical Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Joseph F. Tomashefski, Chief of Research and Director, Cardio-Pulmonary Laboratory, Ohio Tuberculosis Hospital, Columbus, Ohio

Moderator: **Edwin R. Levine**, Assistant Professor of Clinical Medicine, Chicago Medical School; Attending Physician, Cook County and Edgewater Hospital, Chicago, Illinois

NOTE: Seating capacity at the Round Table Luncheons is limited and reservations will be accepted in the order received.

Afternoon Session

1:55 p.m.—SCIENTIFIC SESSION—Washington Room

Co-Chairmen: **M. Jay Flipse**, Miami, Florida
Carl H. Gellenthien, Valmora, New Mexico

2:00 p.m.—*The Interrelation of Pulmonary and Esophageal Disease*
Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois

2:15 p.m.—*Discussor:* **Arthur M. Olsen**, Professor of Medicine, Mayo Foundation, University of Minnesota Graduate School of Medicine, Rochester, Minnesota

2:20 p.m.—*Discussion from the floor*

2:25 p.m.—*Surgery in Aortic Valve Disease*
Charles A. Hufnagel, Professor of Surgical Research, Associate Professor of Surgery and Director of the Experimental Laboratory, Georgetown University Medical Center, Washington, D. C.

2:40 p.m.—*Discussor:* **David H. Waterman**, Chief, Thoracic Surgery, Fort Sanders Presbyterian Hospital, Knoxville, Tennessee

2:45 p.m.—*Discussion from the floor*

2:50 p.m.—*Modern Radiotherapy of Bronchogenic Carcinoma*
Milton Friedman, Associate Professor of Radiology, New York University College of Medicine, New York City

3:05 p.m.—*Discussor:* **Edgar Mayer**, Clinical Professor of Medicine, New York University Postgraduate Medical Center, New York City

3:10 p.m.—*Discussion from the floor*

3:15 p.m.—*Traumatic Heart Disease*
John S. LaDue, Assistant Professor of Clinical Medicine, Cornell University Medical College, New York City

3:30 p.m.—*Discussor:* **Benjamin Manchester**, Assistant Clinical Professor of Medicine, The George Washington University School of Medicine, Washington, D. C.

3:35 p.m.—*Discussion from the floor*

3:40 p.m.—*Intermission*

3:55 p.m.—*Cytologic Findings in Non-Malignant Chest Diseases*
Seymour M. Farber, In Charge, University of California Tuberculosis and Chest Service, San Francisco, California

4:10 p.m.—*Discussor:* **Edith E. Sproul**, Associate Professor of Pathology, Columbus University College of Physicians and Surgeons, New York City

4:15 p.m.—*Discussion from the floor*

4:20 p.m.—PANEL DISCUSSION

"The Evaluation of Cardiac Disability"

Moderator: **Coleman B. Rabin**, Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City

Panel: **Irvin Klein**, Associate Compensation Examining Physician, Workmen's Compensation Board, New York State

Norman O. Rothermich, Clinical Associate Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

F. Mason Sones, Jr., Director, Heart Catheterization Laboratory, Department of Cardiovascular Disease, The Cleveland Clinic, Cleveland, Ohio

Evening Session

6:00 p.m.—COCKTAIL PARTY—Madison Room

By courtesy of the Pennsylvania Chapter

7:00 p.m.—DINNER—Adams Room

Burgess L. Gordon, Albuquerque, New Mexico
President, American College of Chest Physicians, *Chairman*

Guest Speaker

"The Challenge to the Medical and Legal Professions"

Robert K. Bell, Ocean City, New Jersey
Past President, New Jersey State Bar Association; Member, House of Delegates, American Bar Association; Economic Ambassador of New Jersey

9:15 p.m.—FIRESIDE CONFERENCES—Washington Room

Hosts: Members, Pennsylvania Chapter, American College of Chest Physicians

Subjects and Discussion Leaders

1) SURGERY OF THE CORONARY ARTERIES

Claude S. Beck, Professor of Cardiovascular Surgery, Western Reserve University and University Hospitals, Cleveland, Ohio

Charles B. Ripstein, Professor of Surgery and Executive Officer, Albert Einstein College of Medicine, Yeshiva University, Chief of General and Thoracic Surgery, Bronx Municipal Hospital Center, New York City

2) RECENT TUBERCULIN CONVERTERS

W. Leonard Howard, Superintendent, William H. Maybury Sanatorium, Northville, Michigan

J. Arthur Myers, Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis, Minnesota

3) MANAGEMENT OF EMPHYSEMA

Andrew L. Banyai, Associate Clinical Professor of Medicine, Marquette University School of Medicine; Clinical Director, Muirdale Sanatorium, Milwaukee, Wisconsin

Herbert C. Sweet, Associate Professor of Internal Medicine and Director, Pulmonary Laboratory, St. Louis University School of Medicine, St. Louis, Missouri

4) CORONARY DISEASE

Arthur Grishman, Assistant Attending Physician for Cardiology, The Mount Sinai Hospital, New York City

Nathaniel E. Reich, Assistant Clinical Professor of Medicine, State University of New York College of Medicine; Attending Cardiologist, Jewish Chronic Disease Hospital, Brooklyn, New York

5) COLLAGEN DISEASES AFFECTING THE LUNGS

Alvis E. Greer, Professor Emeritus of Clinical Medicine, Baylor University College of Medicine, Houston, Texas

Eli H. Rubin, Professor of Clinical Medicine, Albert Einstein College of Medicine, Yeshiva University; Chief, Pulmonary Division, Bronx Municipal Hospital Center, New York City

6) ASTHMA

Leon Unger, Associate Professor of Medicine, Northwestern University Medical School; Attending Physician, Cook County Hospital, Chicago, Ill.

7) THE PLACE OF BCG IN THE CONTROL OF TUBERCULOSIS

Milton I. Levine, Associate Professor of Pediatrics, Cornell University Medical College; Associate Attending Pediatrician and Director, Children's Pulmonary Clinic, New York Hospital, New York City

George G. Ornstein, Professor of Medicine, New York Polyclinic Hospital Medical School, New York City

8) CONGESTIVE HEART FAILURE

Louis F. Bishop, Assistant Clinical Professor of Medicine, New York University College of Medicine; Attending Cardiologist, Veterans Hospital, Kingsbridge, New York

Paul D. Camp, Assistant Professor of Clinical Medicine, and Chief, In Charge, Adult Cardiac Clinic, Medical College of Virginia, Richmond, Va.

9) CHEMOTHERAPY IN PULMONARY DISEASE

Edward Dunner, Secretary, VA-Armed Forces Committee on the Chemotherapy of Tuberculosis, Veterans Administration, Washington, D. C.

Alfred Goldman, Associate Professor of Clinical Medicine, and Director, Medical Chest Clinic, Washington University School of Medicine, St. Louis, Missouri

10) BRONCHIECTASIS

Daniel C. Baker, Jr., Surgeon-Director, Manhattan Eye & Ear Infirmary; Bronchoesophagologist, First Surgical Division (Thoracic Surgery), Bellevue Hospital, New York City

Arthur C. White, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

11) HYPERTENSION

Irving Graef, Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School; Attending Physician, 4th Medical (New York University) Division, Bellevue Hospital, New York City

Maurice A. Schnitker, Director of Medicine and Chief, Medical Service, St. Vincent's Hospital, Toledo, Ohio

12) SURGERY OF LUNG TUMORS

Edgar W. Davis, Professor of Thoracic Surgery, Georgetown University School of Medicine, Washington, D. C.

William L. Watson, Professor of Clinical Surgery, Cornell University Medical College; Chief, Thoracic Service, Memorial Center for Cancer and Allied Diseases, New York City

13) COR PULMONALE

Robert B. Durham, Chief Cardiologist, Shore Memorial Hospital (Somers Point); Chief, Cardiac Clinic, Atlantic City Hospital; Medical Chief, Atlantic City Beach Patrol, Atlantic City, New Jersey

Gerard M. Turino, Cardio-Respiratory Laboratory, Columbia-Presbyterian Medical Center, New York City

14) PSYCHOSOMATIC ASPECTS OF PULMONARY DISEASE

J. D. Matis, Associate Attending Physician, Beth David Hospital, New York City

Emil Rothstein, Instructor in Medicine, Tufts University College of Medicine; Editor, NP-Tuberculosis Newsletter, Veterans Hospital, Brockton, Massachusetts

NOTE: The Fireside Conferences are informal and offer an opportunity for free discussion. Discussion leaders will be seated at tables with proper identification. Physicians may participate in the discussion of their choice, or move on to other discussions when and if they desire. Refreshments will be served.

ADMINISTRATIVE SESSIONS

Tuesday, December 3, 1957

EXAMINATIONS FOR FELLOWSHIP

The Board of Examiners will conduct oral and written examinations for Fellowship in the American College of Chest Physicians at the Warwick Hotel, Philadelphia, on Tuesday, December 3, 1957.

Candidates are requested to report at 8:30 a.m. at the examining room, as indicated on the hotel bulletin board. The written examinations will be held in the morning and the oral in the afternoon.

David B. Radner, Chicago, Illinois
Chairman, Board of Examiners

EXECUTIVE SESSIONS

10:00 a.m.—Executive Council Meeting

Burgess L. Gordon, Albuquerque, New Mexico, *President*

12:00 noon—Luncheon

Joint Meeting, Board of Governors and Board of Regents

David H. Waterman, Knoxville, Tennessee, Chairman, Board of Governors

2:30 p.m.—Semi-Annual Meeting, Board of Regents

John F. Briggs, St. Paul, Minnesota, *Chairman*

COUNCIL AND COMMITTEE MEETINGS

Special meetings of councils and committees will be held as scheduled, beginning at 9:00 a.m. The rooms in which these meetings are to be held will be posted on the hotel bulletin board.

FOR RESERVATION FORM SEE PAGE XXV

NEW CHAPTER OFFICERS

COLORADO CHAPTER

President	Albert Guggenheim, Denver
Vice President	James A. Wier, Denver
Secretary-Treasurer	LeRoy Elrick, Denver (re-elected)

INDIANA CHAPTER

President	George S. Bond, Indianapolis
Vice President	W. Donald Close, Indianapolis
Secretary-Treasurer	Donald F. MacLeod, Indianapolis

KENTUCKY CHAPTER

President	J. Ray Bryant, Louisville
Vice President	Walker Porter Mayo, Lexington
Secretary-Treasurer	Daniel N. Pickar, Louisville

PENNSYLVANIA CHAPTER

President	Katharine R. Boucot, Philadelphia
Vice President	Edward M. Kent, Pittsburgh
Secretary-Treasurer	Robert L. Mayock, Philadelphia

College Chapter News

HAWAIIAN CHAPTER

College members welcome Murray Kornfeld to Honolulu. (left to right) Dr. Hastings H. Walker, Regent; Mr. Murray Kornfeld, Executive Director; Dr. Frederick L. Giles, Secretary, Hawaiian Chapter; Dr. Edmund L. Lee.

A meeting of the members of the Hawaiian Chapter was held in Honolulu September 26, at which time Mr. Murray Kornfeld, Executive Director of the College, discussed College activities. The chapter plans to organize a scientific and social program for College members who will participate in the post-congress tour to include Hawaii in connection with the Fifth International Congress on Diseases of the Chest to be held in Tokyo, Japan, September 7-11, 1958. The dates for the Hawaii meeting will be announced in a future issue of the journal as soon as the arrangements have been completed.

Mr. Kornfeld also visited Dr. William F. Leslie, Governor of the College for the Hawaiian Islands, in Hilo.

HONG KONG AND CHINA CHAPTER

Members of the Hong Kong and China Chapter met at the Ruttonjee Sanatorium, Hong Kong, on September 13. Dr. Li Shu-Fan, Regent, presided and presented a Fellowship certificate to Dr. A. S. Moodie. Dr. Eung Soo Han, Seoul, Korea, Governor for the College and Minister of Health for South Korea, presented a lecture on "Control of Tuberculosis in Korea."

LOUISIANA CHAPTER

The Louisiana Chapter will hold its semi-annual meeting at the Veterans Administration Hospital, New Orleans, on December 6. The following program will be presented beginning at 2:00 p.m.:

"Physiologic Manifestations of Alveolar Hypoventilation"
Alfred P. Fishman, New York City

"Current Aspects in the Surgical Treatment of Acquired Cardiac Disease"
Charles A. Beskin, New Orleans

Business meeting

NEWS NOTES

Dr. Burgess L. Gordon, President of the American College of Chest Physicians, has been appointed Director of Medical Education and Executive Secretary of the Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico. He has taken over his duties in Albuquerque and is engaged in developing the residency training program at the Lovelace Foundation. Members of the College who know of candidates interested in the various openings at the Foundation are invited to communicate with Dr. Gordon.

Drs. Ite Boerema, Amsterdam, Holland; **Juan Netto,** Asuncion, Paraguay; **Shigeru Sakakibara,** Tokyo, Japan; and **Jorge Taiana,** Buenos Aires, Argentina, participated in the 22nd Congress of the International College of Surgeons held in Chicago, September 8-12. These Fellows of the College are visiting important clinics in the United States concerned with cardiovascular and thoracic diseases. Several of them took time from their busy schedules to pay a visit to the Executive Offices of the College in Chicago.

By unanimous resolution of the South African National Tuberculosis Association, the Executive of the Cape Tuberculosis Council has named its new center the D. P. Marais S.A.N.T.A. Centre in recognition of the long and faithful devotion and close association of **Dr. David P. Marais** with the tuberculosis campaign in South Africa. Dr. Marais, of Cape Town, is Regent of the College for South Africa.

Dr. Alvan L. Barach, New York City, Chairman of the Council on Research, spoke on "Pulmonary Emphysema and Bronchiectasis; Physiological and Clinical Aspects" before the Barcelona Chapter of the College and the Royal Academy of Medicine in Barcelona, Spain on July 8. The meeting, arranged by **Dr. Antonio Caralps,** Regent of the College for Spain, was attended by a large number of physicians in the Barcelona area. His paper will be published in the Abstracts of the Royal Academy.

Dr. Benedict R. Walske, formerly Chief of Surgical Services at the Veterans Administration Hospital, Lincoln, Nebraska, has been appointed Associate Professor of Surgery, Acting Director of the Department of Surgery, and Head of Surgical Specialties at Creighton University School of Medicine, Omaha.

Dr. John C. Parsons, Des Moines, Iowa, was given a distinguished service medallion by the Iowa Heart Association recently.

Fellows of the College who participated in the Tennessee Valley Medical Assembly held in Chattanooga recently were **Drs. Chevalier L. Jackson,** Philadelphia; **Samuel A. Thompson,** New York City and **Paul Dudley White,** Boston.

Obituary

RAY HOYT BIGGS

1906 - 1957

Dr. Ray Hoyt Biggs expired at the Mississippi State Sanatorium on July 12, 1957, following a lengthy illness.

Dr. Biggs was born in Jackson, Mississippi on October 7, 1906. He received his elementary and high school education in the city schools of Jackson. He was graduated from the University of Alabama in 1928, with a B.A. degree. He obtained his medical certificate from the University of Mississippi in 1931, his M.D. degree from Emory University in 1933, and interned at Fitkin Memorial Hospital, Neptune, New Jersey. He was awarded a Master of Public Health degree by Johns Hopkins University in 1938.

While serving as Madison County Health Officer at Canton, Mississippi, he developed pulmonary tuberculosis and entered the Mississippi State Sanatorium for treatment in 1938. After his disease was arrested in 1939, he joined the staff of the sanatorium. In 1944, he was appointed Assistant Superintendent and Medical Director.

Dr. Biggs' professional life was characterized by integrity and intelligence, and complete devotion to the welfare of his patients. His opinions were highly valued by his professional colleagues. He was author of several scientific papers, published both in local and national journals. He was a member of the Central Medical Society, the Mississippi Medical Association, the American Medical Association, the American Trudeau Society, and the American College of Chest Physicians. He was a deacon of the Presbyterian Church.

Dr. Biggs was married to Edwina Ailene Ozier on September 21, 1932. To them was born one daughter, Edwina Patricia Biggs. He is survived by his mother, Mrs. C. E. Biggs, his widow and his daughter.

Clyde A. Watkins, M.D.

Book Review

TOPOGRAPHISCHE AUSDEUTUNG DER BRONCHIEN IM ROENTGENBILD UNTER BESONDERER BERUECKSICHTIGUNG DES RAUMFAKTORS by Claus Esser, Georg Thieme, Stuttgart, 1957 (Second edition, 210 pages, $13.50)

This book represents a remarkable, lucid and comprehensive study of the bronchi, which should be of interest to specialists in chest diseases. It offers an entirely new approach to clinico-anatomic orientation, with particular reference to various units of the lung. It portrays in a crystal-clear manner the basic pattern of the lower air passages. Excellent schematic diagrams, beautifully reproduced bronchograms and tomograms are instrumental in conveying the purported information of this volume. Salient aspects of developmental anatomy are adequately dealt with. Due recognition is given in the text to terminology in preferential usage as well as to that proposed by other authors. The exposition of the whole subject is thoroughly covered. Meticulous attention to details and profuse illustration of all pertinent items render this monograph an outstanding contribution to current medical literature. Topographic guides and easily comprehensible coding add to the satisfactory perusal of this work. The format, quality of paper, printing and binding are of high quality.

Andrew L. Banyai, M.D.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Tuberculosis specialist, age 44, F.C.C.P., now chief of 336-bed tuberculosis service, would like to work in a sanatorium in the general area of New York City or New Jersey for 6 months. Please address inquiries to Box 294B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Chest physician, F.C.C.P., graduate of approved American school, 16 years' experience in diseases of chest, age 43, married, presently medical director and superintendent of 110-bed tuberculosis hospital, seeks similar position in the south or southwest. Please address inquiries to Box 295B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Board eligible internist wanted for Florida State Tuberculosis Hospitals. Rapidly developing program with opportunities for advancement. Beautiful hospitals. Furnished houses available. Liberal retirement and other benefits. Salary dependent upon qualifications. Write: Roberts Davies, M.D., Director, State Tuberculosis Board, P.O. Box 286, Tallahassee, Florida.

Associate physician wanted for approved chest disease hospital to assist in supervision of patient care. Must be eligible for California license. Salary $9600 to $10,000 per annum start. Please address inquiries to Box 292A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Assistant physician wanted for tuberculosis hospital. Must be eligible for California license. Salary $8400 per annum. Please address inquiries to Box 293A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Resident surgeon wanted for 500-bed tuberculosis hospital with active thoracic surgery department. Apply giving details of training to Medical Director, Southeast Florida Tuberculosis Hospital, Box 1411, Lantana, Florida.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Interim Session and Semi-Annual Meetings
Board of Regents and Board of Governors
American College of Chest Physicians
Warwick Hotel, Philadelphia, December 2-3, 1957

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1957

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSES

3rd Annual Postgraduate Course on Diseases of the Chest
Ambassador Hotel, Los Angeles, December 9-13

11th Annual Postgraduate Course on Diseases of the Chest
Warwick Hotel, Philadelphia, March 3-7, 1958

CHAPTER MEETINGS

Southern Chapter, Miami Beach, Florida, November 10-11
Louisiana Chapter, New Orleans, December 6

ADVANCE REGISTRATION AND RESERVATION FORM

American College of Chest Physicians

112 East Chestnut Street

Chicago 11, Illinois

Please find enclosed my check in the amount of $_____ for reservations at the following functions to be held in Philadelphia on Monday, December 2, 1957.

ROUND TABLE LUNCHEONS

$3.75 each

1) **Present and Future Developments in Heart Surgery**
2) **Long Term Results of Chemotherapy in Tuberculosis**
3) **Anticoagulant Therapy in Acute and Chronic Coronary Heart Disease**
4) **Inhalation Therapy**

First Choice No._____ Second Choice No._____

DINNER

$6.00 each

Please reserve_____ places at the dinner.

Applications for reservations at the Round Table Luncheons will be accepted in the order received. Your luncheon and dinner tickets will be available at the College Registration Desk, Walnut Room, Warwick Hotel, Philadelphia, on Monday morning, December 2. Please make checks payable to the AMERICAN COLLEGE OF CHEST PHYSICIANS.

Name_____

Address_____

City and State_____

Please Return This Form Promptly.
Thank you.

PLAN A TRIP TO TOKYO

For The

FIFTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Sponsored by the Council on International Affairs
American College of Chest Physicians

Presented under the Patronage of the
Government of Japan

TOKYO, JAPAN **SEPTEMBER 7-11, 1958**

President
Prof. Taizo Kumagai

Vice-Presidents
Prof. Hiroshige Shiota
Prof. Yoneji Miyagawa
Prof. Seizo Hatsunuma
Prof. Arao Imamura
Prof. Yas Kuno

Executive Officers
Prof. Masanaka Terada
Prof. Osamu Kitamoto
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Taizo Ishizaka, Chairman

Secretary General
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A Pre-Congress Tour of Japan

4 days—
KYOTO
NARA
NUMAZU
HAKONE
KAMAKURA

Diabutsu (Great Buddha), Kamakura

And The Post-Congress Tour

15 days

With planned scientific programs, social events and sightseeing . . .

arranged by College Chapters in . . . **HONG KONG**
BANGKOK
MANILA
HONOLULU

Upon completion of arrangements for the tours, a printed brochure containing all pertinent information will be made available this fall by Cartan Travel Bureau, Inc., Chicago, official travel agency for the Congress.

For further information please write to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois

THE EDITORIAL BOARD

FOR

DISEASES OF THE CHEST

is pleased to announce . . .

SECTION ON CARDIOVASCULAR DISEASES

to be published in each issue of the College Journal

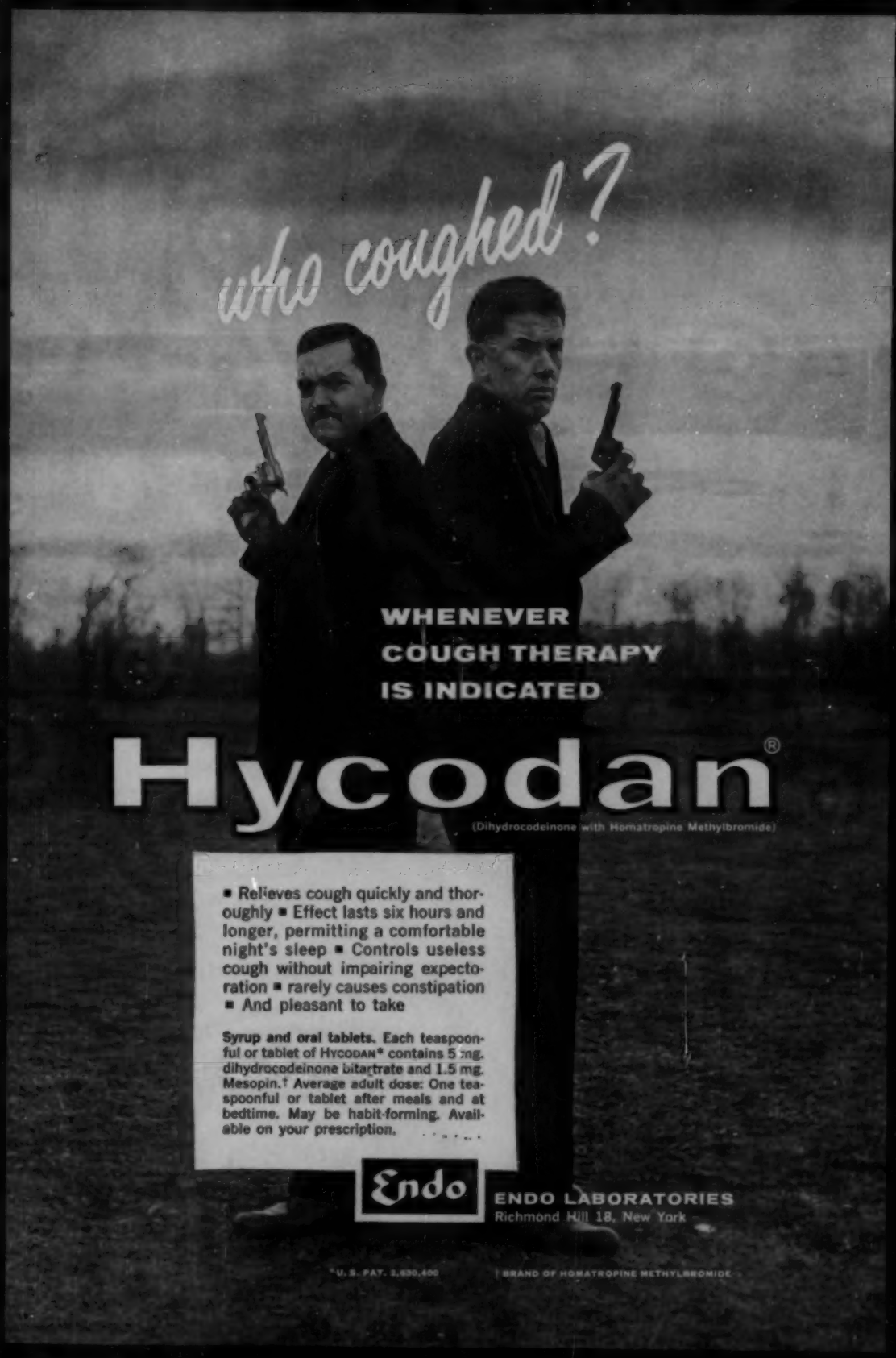
DISEASES OF THE CHEST

effective

JANUARY, 1958

This new Section is being established because of the growth of the College and the varied interests of its members. The new Section will facilitate the selection of scientific papers of significance to our readers. The Editorial Board welcomes recommendations at all times relative to the improvement and maintenance of the high standards of the Journal.

J. Arthur Myers, M.D.
Editor-in-Chief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■ Relieves cough quickly and thoroughly ■ Effect lasts six hours and longer, permitting a comfortable night's sleep ■ Controls useless cough without impairing expectoration ■ rarely causes constipation ■ And pleasant to take
Syrup and oral tablets. Each teaspoonful or tablet of HYCODAN* contains 5 mg. dihydrocodeinone bitartrate and 1.5 mg. Mesopin.† Average adult dose: One teaspoonful or tablet after meals and at bedtime. May be habit-forming. Available on your prescription.
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